THE EVALUATION OF LUNG FUNCTION IN RURAL DWELLING CHILDREN

A Thesis Submitted to the College of Graduate Studies and Research In

Partial Fulfillment of the Requirements For the Degree of Master of Science

In the Department of Community Health and Epidemiology

University of Saskatchewan

by

Lakshmi Balakrishnan

Abstract

Background:

Asthma severity indicators and their risk factors are understudied in the farming and non-farming populations. Further study is needed. Our objective was to evaluate rural exposures and pulmonary function in a rural pediatric population and their relationships.

Methods:

For this study, data from the Saskatchewan Rural Health Study (SRHS) child component was used. SRHS is a population-based study, conducted in 2011, evaluating the health of rural dwelling residents in the province of Saskatchewan, Canada. The SRHS is designed as a cohort study. However, the data used for this analysis is from the baseline data collection. The initial data collected included a parent-completed survey questionnaire answered on behalf of the child. From this study sample, a subset of children (6-14 years old) was selected to participate in clinical testing, which included anthropometric measures and pulmonary function testing (PFT) using spirometry (n=584). PFTs followed ATS criteria and all statistical analyses were controlled for child age, sex, and height.

Results:

Among children participating in the clinical testing, 47.5% were female and 54.5% lived on a farm. Of those living on farms, 77.5% were livestock farms. The mean percent predicted value (PPV) for Forced Expiratory Volume in 1 second (FEV_1) and forced vital capacity (FVC) among those living on the farm were 104.8% and 105.4%, respectively while the mean PPV for FEV_1 and FVC among the non-farm dwellers were 102.7% and 101.4%, respectively. After adjustment for potential confounders using linear regression, higher FEV_1 ($p=0.03$) and FVC ($p=0.006$) were seen among farm dwelling children while there was a trend towards lower FEV_1/FVC ratio ($p=0.09$) among farm dwellers compared to non-farm dwellers. Higher FVC and lower FEV_1/FVC ratio were also seen with children who regularly emptied grain bins ($p<0.05$). Trends towards a higher FEV_1 ($p=0.14$) and FVC ($p=0.08$) were also seen with children living on a farm in the first year of life.

Conclusion:

Differences in lung function were seen between farm and non-farm rural dwelling children and certain farming activities, specifically, emptying grain bins. Despite

a higher FEV_1 and FVC among farm dwellers, the FEV_1/FVC ratio was lower compared to non-farm dwellers. A trend towards a higher FEV_1 and FVC was also seen with living on a farm in the first year of life suggesting that differences in lung function seen in farm dwelling children may not be purely due to reverse causality.

Co-Authorship

This thesis represents the work of Lakshmi Balakrishnan in collaboration with her supervisor, Dr. Joshua Lawson from the University of Saskatchewan, as well as additional co-authors on the thesis manuscript, "The Evaluation of Lung Function in Rural Dwelling Children". Dr. Balakrishnan and Dr. Lawson were involved in the formation of the research questions as well as the completion of the data analysis, interpretation of results and preparation and revision of the manuscript for the current analysis. Dr. Balakrishnan was responsible for partial cleaning of the dataset. Dr. Lawson provided suggestions, guidance and editorial input into the creation of the manuscript. Dr. Lawson, Dr. Rennie, Dr. Pahwa, Dr. Karunayake and Dr. Dosman were involved with the conception and design of the initial study, completion of the data collection, and critical review and editing of the manuscript.

Acknowledgements

I would like to express my gratitude toward those who guided and supported me throughout this process. First and foremost, I would like to thank my supervisor, Dr. Lawson, for his guidance and support during this thesis. His expertise, thoughtful insight, and constructive and timely feedback were invaluable toward the completion of this thesis. Not enough can be said toward his leadership, patience and wise counsel.

Next, I would like to thank the Saskatchewan Rural Health Study team and the Estevan Cohort Study team at the University of Saskatchewan. I am grateful for the efforts of Dr. Rennie, Dr. Dosman, Dr. Pahwa, and Dr. Karunanayake, who reviewed the manuscripts in this thesis and I thank them for the constructive feedback.

I would also like to thank the Clinical Investigator's Program for the financial support I received and the opportunity to present this work at the 2015 American Thoracic Society Meeting. It was an amazing experience. I would especially like to thank Dr. Gary Groot, Dr. John DeCoteau and Ms. Angie Zoerb for their support and encouragement through the pursuit of my Masters. This program complemented my thesis and served to deepen my interest in rural and community health.

I would like to thank the Department of Surgery and the General Surgery Resident Program for being so understanding and accommodating in my pursuit for further education.

Fifth, I would like to thank the faculty and staff members in the Department of Saskatchewan Community Health and Epidemiology at the University of Saskatchewan for creating a supportive and positive atmosphere. Special thanks to the outstanding instructors of these courses. I would also like to thank my classmates and those belonging to the Rural Health Study Research Group. Your passion for learning and epidemiology is contagious. Thank you for listening to my practice presentations and giving such helpful feedback.

Finally, I would like to thank my family (Amma, Appa, Divya and Kyler) and friends for their love, encouragement, patience and unwavering support. Words cannot express how much your presence in my life and support mean to me. I would like to dedicate this Masters to my loving father, for all his love, support, and passion in academic pursuit. I miss you and love you everyday and carry you in my heart always.

Table of Contents

List of Tables

CHAPTER 1:

INTRODUCTION

Asthma is a rising global problem. According to the World Health Organization (WHO), in 2010, 235 million people suffered from asthma. (1) It is the most common chronic condition in children. (1,2) Asthma is also one of the most common chronic airway diseases in North America. In recent decades, its prevalence has been increasing and its impact can be seen in Canada. (2,3) In 2000 – 2001, the prevalence of asthma in Canada was approximately 13%. (2,3,) The prevalence of asthma has increased, but according to the same report, the frequency of asthma attacks has decreased. It has been suggested that this has been the result of increasing prevalence but less severe disease. (1) More recent literature has shown that asthma severity and morbidity may be underestimated. (3) Diagnosing and subsequent management patterns can affect the well-being of those with asthma. Accurate diagnosis and severity assessment are important for proper asthma management. A better understanding of asthma is needed in order to address these problems and improve asthma prevention and treatment.

In Canada, a significant proportion of the population (20%), lives in rural and farming areas. (2) This proportion is even greater in Saskatchewan, where this percentage rises to 30%. (2) Some have, however, suggested that the prevalence of asthma is lower in rural populations in comparison to urban populations. (1,4 – 9) Despite this, research that has been completed in Canada has shown that asthma prevalence in rural populations is still relatively high and would still be considered a substantial problem. (4,8) Many of these same exposures with higher levels in rural and farm locations that have been suggested to protect from asthma, such as endotoxin, have also been associated with higher asthma severity among those who have asthma. (9-15) However, little is known about the true extent of asthma severity in rural populations and there is a need to study this further as this information can play an important role in assessing the efficacy of asthma diagnosis and asthma management.

The utilization of objective measures, like pulmonary function testing, may provide greater insight into lung health and asthma's impact on underlying lung health. Pulmonary function testing, through methods of spirometry, is a reliable, easily reproducible, objective measure of respiratory health. Spirometry has been primarily used for evaluating pulmonary function in adults. It is a useful measure for pediatric respiratory health. Children present a unique challenge with spirometry in terms of appropriate maneuvers and interpretation of test values. (16) With the appropriate maneuvers, and skilled technicians, spirometry can result in high yield and high quality results for interpreting pediatric respiratory health.

Spirometry allows for assessment of different factors that affect respiratory health, and what the true impact of these factors is on disease severity. This can influence and allow for improvement of treatment and disease control. Despite the usefulness of lung function testing through spirometry in the assessment of lung health, especially in how it relates to asthma, there are few studies that have considered objective measures of lung health in rural populations.

Given the importance of investigating lung health among children, the large proportion of rural dwellers in Saskatchewan, and the gaps regarding the investigation of lung function in rural settings, the overall purpose of my thesis will be to investigate pulmonary function in a rural Canadian population.

This thesis has been laid out in a specific manner in order to include a manuscript. Chapter 2 includes a literature review and ends with the rationale for the study and research questions. Chapter 3 describes the background of the overall study and the methods as well as preliminary results to help describe the study population. Chapter 4 is the manuscript submitted for publication. Finally, Chapter 5 is a summary and discussion chapter that highlights the findings and frames the results in a broader, epidemiological perspective not possible in the manuscript.

CHAPTER TWO:

LITERATURE REVIEW

2.1 Scope of the Literature Review

The purpose of this chapter is to explore the current literature that has examined pulmonary function and pediatric asthma when considering rural populations. The main outcome under study is pulmonary function. In this literature review, pulmonary function will be described with regard to its technique and application. Asthma, the most common respiratory illness among children, will also be defined with its triggers and potential risk factors outlined and discussed in relation to the use of lung function assessment as part of the disease evaluation. Literature that supports the use of pulmonary function for assessment and study of respiratory disease will be summarized. The literature regarding farming activities and farming exposure and the impact on asthma and asthma severity, including lung function, will also be reviewed.

2.2 Methods of the literature review

The literature review was conducted using time parameters between 1995 and 2016. A combination of sources was utilized including Pub Med, Google Scholar and the University of Saskatchewan Library search engines. These were used to identify evidence contained in existing scientific publications and reports. The literature review was conducted using search terms including a combination of key words such as “asthma”, “pediatric”, “rural”, “Canada”, “farm”, “child”, “pulmonary function testing”, “FEV_1”, “FVC”, “FEV/FVC”, “$FEF_{(25-75)}$”, “ISAAC study”, “farming activity”, “children”, “asthma severity”, and, “asthma symptoms”. Scientific articles in the reference section of previously read scientific papers were also identified and reviewed. Papers selected for the literature review were available in English and published after 1995. Most of the selected publications were cohort or cross-sectional in design and originated from North America, Europe, and Australia.

2.3 Respiratory Health

Respiratory health is an important area for study, especially in the pediatric population. Children are a susceptible population for respiratory illness and more prone to be affected and hospitalized for these illnesses. (1) Respiratory illness is one of the most common acute and chronic presentations of children to a primary health care provider. These include, but are not limited to asthma, rhinitis, hay fever, wheeze and recurrent pulmonary infection.

Many factors can impact developing lungs and their function, and therefore influence the presence and severity of respiratory diseases. The lungs have a large surface area where pollutants or allergens in the environment can be readily absorbed and impact lung function and physiology. Children have immature, developing lungs that are more susceptible to environmental exposures and allergens that may irritate the lungs and make one more prone to respiratory illness or may impair future lung function. (3)

Having a good understanding of lung health and pulmonary function is key to being able to understand respiratory illness in both adult and pediatric populations. This includes using accurate methods for measuring and assessing lung health. These methods are necessary to be able to evaluate lung health, the impact of respiratory illness, and help decide between management options. Pulmonary function testing using spirometry is one such effective objective measure of lung health.

2.4 Lung Function Testing

Pulmonary function tests are a group of tests that measure how effectively the lungs inhale and exhale air and how well they transfer gases such as oxygen from the atmosphere into the body's circulation. Spirometry is one method of pulmonary function testing. Testing can be performed using a spirometer, which measures volume and airflow. To use a spirometer, a subject would breathe into a mouthpiece connected to the spirometer. Usually, this is done using a nose clip to ensure maximal respiratory effort through the mouth. Then measurements of the volume of air exhaled and how quickly air is exhaled over a period of time are taken. Spirometry can be used to evaluate a wide range of lung diseases. Spirometry can be utilized for diagnosis of lung disease, to measure severity of these conditions, and to evaluate efficacy of treatment of lung disease. Some of the maneuvers with spirometry measure passive regular breathing, while others require forced exhalation after a deep breath.

Important measurements of pulmonary function can be obtained using spirometry through the forced expiratory maneuver. These include forced vital capacity (FVC), forced expiratory volume (FEV_1), and forced expiratory flow between the 25th and 75th percentile of FVC ($FEF_{25\text{-}75\%}$). FVC measures the volume or amount of air one can exhale forcefully after deep inhalation. FEV measures the volume or amount of air one can forcefully exhale in one breath over a measured time, typically in the first second (FEV_1). The ratio of FEV_1 and FVC (FEV_1/FVC) can provide a useful measure for evaluating obstructive and restrictive lung disease. A decrease in the ratio resulting from a decreased FEV_1, is seen with obstructive lung disease. Therefore, a disease such as chronic obstructive pulmonary disease (COPD) would have a reduced (FEV_1/FVC) ratio. In restrictive disease, both FEV_1 and FVC are reduced, so the ratio may be normal or even increased. The ratio of (FEV_1/FVC) allows for the ability to diagnose and determine severity of these pulmonary disease processes. $FEF_{25\text{-}75\%}$ measures the rate of air flow between 25 and 75% expiration through an exhalation. It is an indicator of flow in the medium and smaller airways. For the evaluation of asthma, spirometry measures are utilized.

Lung function measures include absolute and predicted values. Absolute values of lung function are the recorded measurements from spirometry for a patient. Predicted values of lung function are predicted for age, sex, and height of a patient, typically based on large population studies of healthy never-smoking patients. Lung function can then be expressed as a percentage of the predictive value by comparing the absolute value to the predicted value. This can allow classification of the severity of impairment in lung function relative to a “normal” population.(16)

Pulmonary function testing through spirometry is performed in a standardized fashion. There are specific guidelines that allow for this standardization and reproducibility of results and to reduce variability from the use of different techniques or equipment. The American Thoracic Society and European Respiratory Society have developed such guidelines. (44) There is a standard to ensure appropriate equipment assessment and maintenance, spirometry calibration and number of spirometry maneuvers performed. (44) Spirometry is performed using a nasal clip with the patient or subject in a seated position. (44) A maximum of eight spirometry maneuvers should be performed. (44) It is important to be able to identify adequate spirometry is performed to be able to utilize the resultant data appropriately. Recognizing the limitations and quality of pulmonary function testing allows for effective interpretation and use of the spirometry results. (48,

51) Comparing results from the different maneuvers to each other and to a calculated range allow for effective comparison and use of the data. (48, 51)

2.5 Lung disease among children

By far, asthma is the most common chronic respiratory condition among children. It often begins in childhood, but asthma episodes can occur at any age. According to the WHO, it is a disease that is characterized by recurrent attacks of breathlessness and wheezing. (1) This can vary in severity and frequency from person to person. Asthma is caused by inflammation of the air passages in the lung and increased sensitivity of the nerve endings in the airway leading to irritability of the airway. It is an obstructive airways disease, where the flow of air in and out of the lungs is limited due to narrowing of the airways. During an asthma episode, the lining of the airways swell causing reduction of air flow in and out of the lungs, usually on expiration, secondary to the narrowing of the airways from the swelling. Many triggers can bring about an asthma attack including allergens, viral respiratory infections, and airborne irritants.

Asthma is one of the most common chronic conditions in the pediatric age group and is responsible for a significant proportion of hospitalization for children under the age of 15 years. (1-5) Effective management of asthma is an important end goal for pediatric health care. In order to accomplish this, a thorough understanding of the disease, its pathophysiology and modifiable risk factors and contributing factors is necessary. In addition to this, it is important to use effective measures of assessment in its evaluation, including spirometry.

2.6 Asthma Diagnosis and Evaluation of Asthma Severity

To diagnose asthma, a thorough history is taken and a physical examination is performed. Spirometry should be used to objectively measure lung volume and airflow and to determine the level of airway obstruction. Changes in spirometry or lung function are the measures that allow for understanding of the underlying disease process.

Indirect methods of measuring asthma severity include symptom report, regular medication use, breakthrough or emergency medicine use, frequency of asthma attacks, degree of exercise tolerance, and lung function as measured by pulmonary function tests. (8,10-15) These measures were based on the development and evolution of the National Asthma Education and Prevention Program (NAEPP) in the 1990's. These measures are also used for the Canadian Asthma Guidelines. (18)

Asthma control is used as part of the evaluation of the efficacy of asthma management. The challenge arises in terms of classifying asthma severity, especially in the pediatric population. Children have a dynamic physiology and it is difficult to know whether they will outgrow their asthma or if the severity will change from a given baseline.(19)

Of the measures used for evaluating asthma severity, pulmonary function testing is the primary objective measure. It is a reproducible measure that is relatively inexpensive and accessible. There has been some controversy in the literature with regard to the role or added benefit of pulmonary function testing in assessing asthma severity in the pediatric population. According to some studies in the 1990's, children may have fairly normal pulmonary function tests that do not correlate with their symptom severity.(10,11) Similar studies also indicated that pulmonary function tests were not as easy to reproduce in the pediatric population, especially for children under the age of seven years. (16,19) A baseline or single pulmonary function test may also be considered a static measure and not allow for good assessment of asthma severity. (16,19) Some studies state that the sensitivity and specificity of serial peak expiratory flow allow for more accurate assessment of asthma. (16) However, the majority of these studies were completed in the assessment of asthma in adult patients. The issues of compliance and technical ability to replicate the pulmonary function testing were minimized due to the population under study who were adult patients with normal cognitive function. However, the ability to reproduce the test can be challenging in the pediatric population.(9) As a result of this challenge, it has been necessary to evaluate if singular or baseline pulmonary function testing would be an appropriate and comparable method of asthma severity assessment or not.

The literature on the use of a baseline pulmonary function test is split. The Canadian Guidelines on the Management of Asthma from the Canadian Thoracic Society (20) are a standardized national guideline that is evidence-based. The most recent guidelines are from January 2012. A persistent decrease in the baseline pulmonary function was associated with the diagnosis of asthma. Pulmonary function testing was found to be easily completed with children age five years and up.(20) Under the age of five, technical and compliance issues arise that may render the results of pulmonary function testing flawed. It is also difficult to discern between asthma and other respiratory illness as the source of decreased pulmonary function in children without careful clinical assessment.

Other studies have shown that a single or baseline pulmonary function testing is a reliable measure for asthma diagnosis and severity. (16,19,21) It is used as the Gold Standard to compare other methods of assessing lung health in children, such as patient/parent asthma questionnaires, breath counting, and exercise tolerance, especially for the ages of 5 years and up.(19-21) A study by Ali et al in 2010 used pulmonary function testing as the standard for comparing measures of breath counting to assess asthma severity in children between the ages of 5 and 18 years.(21) Baseline pulmonary function was used as the standard for comparison because it is a minimally invasive method that has been established in clinical medicine and the literature as a reliable assessment of asthma severity.

A study by James Stout, et al. in 2006 evaluated whether or not the addition of pulmonary function testing changes the classification of asthma severity. (16) The study was a combined cohort study using multi-center populations from two different but related studies on asthma. Cohort 1 was the National Cooperative Inner-City Asthma Study (NCICAS) from 1993-1994 while cohort 2 was the Inner-City Asthma Study from 1998 to 2001. The classification for asthma was mild intermittent, mild persistent, moderate persistent, and severe persistent based on symptom frequency and spirometry [FEV_1 or peak expiratory flow (PEF) measurements]. In cohort 1, 22.8% of the participants and in cohort 2, 27.7% would have been reclassified to a higher class of asthma severity as a result of the pulmonary function testing. These participants were reclassified from mild intermittent asthma class to moderate or severe persistent asthma.

There has been a more recent study that has validated the reproducibility of pulmonary function testing and its correlation to pediatric asthma severity when controlled for patient age, height and weight, or Body Mass Index (16, 19) In the study by Stout et al., asthma severity distribution was assessed for study subjects by asthma symptom frequency and then by spirometry.(16) These severity distributions were then compared. Once spirometry was evaluated in addition to asthma symptom frequency, approximately one third of the participants were re-classified into higher asthma severity categories. The use of a specific objective measure allows for more reliable and consistent data when evaluating asthma.

Improved technology and techniques for performing pulmonary function testing also increases the ability to replicate test results.

2.7 Impact of respiratory disease

Asthma is the most common chronic respiratory disease among children. It is a significant community health issue. Asthma still continues to be a major reason for pediatric hospitalization in Canada. An estimated 235 million people around the globe suffer from asthma and this number is rising.(1,4) It is estimated that the number of people suffering from asthma will grow by more than 100 million worldwide by 2025.(1,4) World-wide, deaths from this condition have reached over 250,000 annually.(4)

In Canada, approximately 20 children and 500 adults die each year from asthma.(2,3) It is estimated that more than 80 per cent of asthma deaths could be prevented with proper asthma education.(4) Despite advances in understanding the disease and the availability of more efficacious medications, asthma is still a major cause of morbidity. This is often a result of under-diagnosis, under-treatment, lack of public understanding and knowledge about the disease, or inadequate asthma education.(4)

Asthma is the leading cause of absenteeism from school and the third leading cause of work loss.(2-5,22,23) Every year in Canada, there are 146,000 emergency room visits due to asthma attacks.(3,5, 22,23) The Conference Board of Canada estimates that in 2010 chronic lung diseases including asthma, lung cancer and chronic obstructive pulmonary disease (COPD) cost $12 billion including $3.4 billion in direct health care costs and $8.6 billion in indirect costs.(5) This combined cost is significant and the exact burden of asthma has been further evaluated. Asthma is the leading driver of children's health care costs at over $2 billion per year.(3, 5,22,23)

Asthma is a treatable disease process with potentially reducible risk factors, and effective measures of asthma control, therefore, actions can be taken to reduce its impact on the population and its demands on healthcare resources. To reduce the impact of asthma, many measures can be taken. Early diagnosis and disease management can reduce the asthma burden on the healthcare system in a significant way. Lung function is a simple, reliable method that can help in this process. The failure to diagnosis asthma and allergic diseases correctly, or in a timely fashion, leads to inadequate disease control and, and as a result, higher treatment costs. (3,5, 22,23) The majority of asthma related costs (95%) are due to poorly controlled asthma.(23) With respect to global health costs, the worldwide economic costs associated with asthma are estimated to exceed those of TB and HIV/AIDS combined according to the WHO. (1)

In a systematic review by Bahadori et al, the indirect and direct costs of asthma were evaluated.(22) The largest component of direct medical costs with asthma initially arose from hospital inpatient care in 1985, and over time, as of

1994, medications have been reported as the largest component of direct medical costs associated with asthma.(22) According to one of the reviewed studies, In the US, the annual estimated cost of asthma was approximately $1.4 billion dollars in 1985 and increased in 1994 to $2.5 billion dollars. The results of the cost assessment of asthma hospitalization in 1994 in Quebec were a total cost of $23.3 million dollars, with pediatric patients accounting for $11 million dollars in cost.(22)

A similar review of asthma health costs was performed in British Columbia by Sadatafavi et al.(23) Data from the BC Linked Health Database and PharmaNet database from 1996 to 2000 was analyzed of the BC population ages five to 55 years of age. The cost analysis included billing information for physician visits, drug dispensations and hospital discharge records. Unit cost was assigned to physician/emergency department visits and government reimbursement fees for prescribed medications were applied. Asthma resulted in $41, 858, 610 dollars in annual health-care related costs during the study period. Medication cost (63.9%) was the largest cost component of total health-care costs associated with asthma in this study. This was followed by physician costs (18.3%) and hospitalization (17.8%).(23)

Education and asthma awareness are also important from a public health policy standpoint to aid in asthma risk reduction. Research and knowledge translation play key roles in increasing public awareness and knowledge with regard to risk prevention and appropriate asthma management. According to the Canadian Asthma Consensus Guidelines (18), the goal of asthma management is to reduce airway inflammation through environmental control measures and the use of regular controller medication, rather than intermittent therapy that is focused on short-term relief of symptoms.

2.8 Asthma Risk Factors

Asthma has many risk factors including personal characteristics (gender, family history, history of allergies, and atopy) and environmental exposures (indoor, outdoor, and occupational exposure). (6, 11,24-40) The strongest risk factors include: a family history of asthma and/or allergy (eczema, allergic rhinitis) (11,24-40); exposure, in infancy, to high levels of antigen such as house dust mites(11, 24-40); exposure to tobacco smoke or chemical irritants in the home or workplace.(6,11, 24-40)

Environmental factors that influence asthma vary by geography. In addition to this, differences in asthma prevalence have been noted between rural and urban populations.(9, 41-43) The rural population requires further study as asthma prevalence and severity may differ between different rural populations, specifically between farming and non-farming populations. Studies have shown that there are differences between farming and non-farming populations regarding protective exposures, atopy, and asthma.(33-41) Von Mutius et al performed a study that found endotoxin was found to be higher in environments, such as homes of farmers, described as protective against the development of asthma and allergies in children. (31) Despite this, not all studies have found differences in asthma prevalence between farm and non-farm dwelling children.(11) Further evaluation of the differences between these populations using methods such as spirometry may help explain differences between study results.

2.9 Asthma Severity/Morbidity

Since, so little is known about the true extent of asthma's severity in rural populations, there is a need for further study of asthma severity and its risk factors. This information can play an important role in assessing the efficacy of asthma diagnosis and asthma management.

While there are some well-conducted studies on asthma, the amount of literature available on asthma severity and morbidity is limited, especially when focusing on rural populations. Rabe et al reviewed global asthma severity and prevalence in a study performed in 2004.(4) It was a collaborative cross-sectional study between many global cities. This cross-sectional study was carried out with data collected from 29 countries where a total of 7786 adults and 3153 children were included. Asthma management was compared to the standard outlined by the Global Iniative for Asthma (GINA). Asthma severity was measured by looking at factors including the use of preventative anti-inflammatory medications, use of quick-relief medication, number of daytime episodes, number of nighttime episodes, and the social effect including absenteeism from school in past 12 months. The utilization of quick relief medication ranged from 9% in Japan to 26 % in Western Europe. Asthma severity was also found to be less in Japan and Asian-Pacific countries, whereas the highest asthma severity was seen in Eastern and Central Europe. This was based on objective and subjective patient perception of asthma control and severity were assessed, including access to medical care, health care use, missed work-school, and medication use.

More recent literature has shown that asthma severity may be underestimated. (4) In the Rabe et al. study, a significant discrepancy also existed between self-perceived asthma severity and objective assessment of asthma severity on the basis of GINA.(4) It was postulated that higher use of preventive medication would be seen with increased asthma severity in controlling asthma. However, the use of anti-inflammatory preventative medications was low across all countries surveyed with high utilization of quick-relief medications, even in patients with severe asthma which suggested poor control of asthma. GINA provides guidelines for management of asthma. The Rabe et al. study indicated that severity was under-estimated and under-treated or poorly controlled when compared to the standard set by the GINA guidelines.

Physician diagnosis of asthma has been considered the gold standard for epidemiological asthma studies. Diagnostic modalities, such as pulmonary function tests (PFTs), are important and have been evaluated as to whether they are comparable to physician diagnosis but are not often used in epidemiological population based research for practical and financial reasons.

Pulmonary function testing has been well established in the assessment of asthma severity for adults and children older than six years of age. Longterm cohort studies have correlated childhood PFT results of children with asthma and asthma severity and pulmonary function impairment in adulthood.(19, 44-46) Forced expiratory maneuvers are used in school children and in adults as the method to perform PFTs. However, this method may not be reproducible in preschool children.(44)

Pulmonary function testing is an important diagnostic tool when evaluating children with asthma.(19) It is an effective and objective method for measuring the degree, location and reversibility of lung compromise in children with asthma, or who may have asthma. It is a useful diagnostic tool for helping confirm the diagnosis of asthma in children with classic or atypical presentations of asthma. It also allows for a method to assess response to therapy and guide management changes.

Diagnosing and subsequent management patterns can affect the well-being of those with asthma. Accurate diagnosis and severity assessment are important for proper asthma management and a better understanding of asthma is needed in order to address these problems and improve asthma prevention and treatment, especially in rural areas where little work on asthma severity has been conducted.

In one rural based study, Lawson et al performed a case-control study of 6 to 18 year old children and adolescents in Humboldt, Saskatchewan and the surrounding area. (28) The study was conducted between 2005 and 2007 during the spring, summer and fall months. Controls were selected from patients without parent reported wheeze or doctor diagnosed asthma. There were 102 cases and 207 controls in the study. Data was collected from standardized questionnaires and lung function while endotoxin exposure was assessed using objective measures of vacuumed dust and tobacco smoke exposure was evaluated using saliva testing for cotinine. Severity and morbidity indicators included doctor diagnosed asthma or the following within the past 12 months; increased wheeze frequency, breathing medication use, sleep disruption from wheeze, and school absenteeism. Findings indicated that high endotoxin levels present in common household areas of rural children with asthma or wheeze may also affect their lung function. These associations may be potentiated by tobacco smoke exposure and female sex and only present among cases.

Oluwole et al. performed a study utilizing pulmonary function, along with skin prick testing and serum IgE levels to determine that micronutrients influenced asthma in rural dwelling Nigerian children.(49) This study was conducted in two phases in 2013. The first phase was a pilot study to obtain descriptive information using survey questionnaires. A total of 1, 071 students completed the surveys. The second phase consisted of clinical testing and analysis. A total of 67 children initially participated in analysis between cases and matched controls. Of these, 46 participated in pulmonary function testing. The study included children between 13 and 14 years old. Pulmonary function testing, along with other clinical measures of skin prick testing and IgE levels were utilized to as objective measures for factors that may impact asthma. The study determined that asthma prevalence was increased compared to what had been previously noted in this region.(49) It had a good study design but a limited number of participants in the clinical study group.

2.10 Predictors of Lung Function

Lung function can be influenced by many factors and these must be adjusted for accordingly. Lung function is known to vary with age, sex and height. (19, 44, 46,) These are accounted for when determining normal ranges of lung function. Lung function may also vary based on one's ethnic background.(19,44, 46) Lung function may also be influenced by weight and body mass index.(19, 44, 46) Other factors that can impact lung function may be demographic, geographic or environmental.(19, 44, 46)

Genetic factors may predict or influence lung function.(44, 46) In children with a family history of asthma, lung function was decreased.(44, 46) Cigarette smoking, occupational and environmental exposures, airways hyper-responsiveness, productive cough, or malnutrition have been seen with a decline in FEV_1.(46) Diet may also influence lung function where intake of antioxidant vitamins may have positive associations with lung function according to some epidemiologic studies. (46) The antioxidants may be protective against the oxidant attack from environmental irritants like cigarette smoke, ozone, and nitrogen dioxide. (46)

Geography and its environmental exposures may also impact lung function. Differences in levels of lung function may exist between rural and urban populations. Priftis et al. hypothesized that urban areas with high rates of pollution would adversely impact respiratory health. (9) His research group performed a study between 1995 and 2004. This eight year study spanned across three separate phases evaluating lung function of children between the ages of 8 – 10 years of age in rural and urban Greece. (35) In phase 1, rural children had lower percent predicted FVC. Lower FVC% growth was seen in the urban compared to rural areas. The study concluded that outdoor air pollutants did not result in increased asthma prevalence. It may cause increased non-specific respiratory symptoms and small airway narrowing as reflected by lower FEF and FVC. Certain pollutants, nitrogen dioxide and sulphur dioxide were increased in the urban areas. The study results suggested long-term exposure to these pollutants in the urban environment impacted pulmonary function and may be associated with sub-clinical airway narrowing. (9)

2.11 Gaps in the Literature

Research has provided many answers and knowledge regarding many aspects of asthma. These include mechanisms of asthma, the prevalence of asthma at the local and international levels, and many risk factors that are associated with asthma. This breadth of knowledge has allowed for further research and understanding into the impact of asthma and developing practical applications pertaining to appropriate asthma diagnosis and management. However, despite the knowledge and understanding obtained from the current literature, many gaps still exist.

Asthma severity and morbidity are significant factors regarding asthma management and are understudied and underestimated in the current literature. Accurate diagnosis and severity and morbidity assessment are important for proper asthma management. This would be important for the study of all populations affected by asthma, especially the rural and pediatric populations since these two populations have a significant burden of disease where true severity has been understudied or not well measured in the current literature. Evaluation of spirometry specific to these populations (i.e. rural dwelling children including those with and without asthma) will help address existing gaps.

Further research into asthma severity and morbidity would offer greater understanding of asthma and has significant implications for improving asthma morbidity reduction and treatment protocols. It is especially important to consider how the limited knowledge of asthma severity and morbidity can impact the rural and farming populations, given that certain rural exposures may aggravate asthma. There may be limitations in health care access in rural areas to provide proper management as well. An understanding of asthma severity and morbidity could significantly impact patient care outcomes by managing the disease appropriately and could reduce morbidity from asthma complications such as exacerbations or asthma attacks.

Most of the asthma literature provides a good understanding about the mechanisms, prevalence, and risk factors of asthma in relation to urban populations. Little is actually known about these factors when evaluating the rural and farming populations, which are unique in their environmental exposures and access characteristics. This mixed picture indicates that further study is warranted to delineate the true extent of asthma and its severity in the rural and farming populations. In Canada, these populations make up a significant portion of the national population and an even greater proportion of the population in Saskatchewan.

2.12 Problem Statement and Rationale:

Agriculture is a necessary part of every nation's economy and a mainstay of many. A large proportion of the Saskatchewan pediatric population lives in rural and farming areas. There are many similarities that exist between these rural areas and those in other parts of Canada making this research important nationally and likely internationally. Research has shown that people living in rural and farming areas may have lower asthma prevalence but these levels are still relatively high, making this a public health concern. (4, 11 26, 27) However, there is limited knowledge regarding the severity and morbidity of asthma in rural populations. This is especially important to consider given that certain rural exposures may aggravate asthma and that there may be limitations in health care access in rural areas to provide proper management. An understanding of asthma severity and morbidity could significantly impact patient care outcomes by managing the disease appropriately and could reduce morbidity from asthma complications such as exacerbations or asthma attacks. Given Canada's large farming and rural-dwelling populations, this data and research may have broad applications and could be expanded upon accordingly.

2.13 **Objectives:**

The overall objective is to investigate pulmonary function in a rural Canadian child population. My specific research questions are:

Lung function outcomes

1. What are the levels of pulmonary function in a rural population of children
2. Are there differences between farm and non-farm dwelling children?

3.a) Are certain types of farming activities associated with pulmonary function after adjusting for potential confounders?

b) Is there interaction between these activities and sex or asthma status?

CHAPTER THREE:

METHODOLOGY

3.1 The Saskatchewan Rural Health Study

The Saskatchewan Rural Health Study (SRHS) is a prospective cohort study with a pediatric and adult component conducted in farming and non-farming rural communities.(47) It was conducted between 2009 and 2015. The purpose of the SRHS is to evaluate respiratory outcomes in rural populations and potential associated health determinants. (47) It consisted of both a questionnaire and clinical testing components including pulmonary function testing. The methods have been published,(47) but I will describe them briefly in this chapter.

3.2 Methodology

3.2.1 Study design

Data from the Saskatchewan Rural Health Study (SRHS) will be used for this analysis. While the SRHS was designed as a cohort study, the data used for this analysis is from the baseline data collection as follow-up data had not yet been collected at the time of this analysis.

3.2.2 Study population

The thesis study population consists of rural dwelling children. These children were between the ages of 6 – 18 years living in rural southern Saskatchewan. Children living in and attending schools in the same rural municipalities (RMs) as the adult portion of the SRHS were eligible. The rural population is defined as being made up of people living in municipalities and towns with a population of 10,000 or less and outside the commuting zone of large urban centers and if the area was at least 60 kilometres from an urban center based on the Statistics Canada definition of rural.

A total of 297 RMs are located in the southern half of the province. The rural study population source within the RMs consisted of taxpaying households located in the RMs and small towns. Purposeful sampling was completed through a multistage, stratified sampling strategy. The initial stratification consisted of dividing southern Saskatchewan into four quadrants (Northwest, Northeast, Southwest and Southeast). This was done to help appropriately represent the province's varied landscapes and industries. A block consisting of 12 adjacent RMs in each quadrant was identified and selected for the study. Some RMs had previously participated in a different large cohort study. These were excluded from the study population to avoid low participation rates due to study fatigue.

A total of 48 of the 297 RMs and 16 of the 145 towns in Saskatchewan were selected for sampling in the study. Randomly generated samples were taken from each quadrant. Each random sample consisted of 9 RMs. Certain households were excluded from the study on the basis of unknown addresses, households outside the study area, duplicates, and deceased household members.

All school divisions with a school in these selected RMs were approached. Each of these participated and were represented in the research. The regions included in the study can be seen in Figure 1. There were 43 schools within these rural areas. The questionnaires were distributed to students in Grades 1 – 12 (ages 6 – 18) through the 39 schools (91% school participation rate) agreeing to participate in the study in 2011. The parents of these children were asked to fill in the survey and return it to the school.

Figure 1: Rural municipalities located in the four study quadrants of the SRHS Study.

A total of 2383 children participated in the baseline survey study. The individual participation rate was 42%. A subset of children was invited to take part in clinical testing which included anthropometric measures, pulmonary funct-

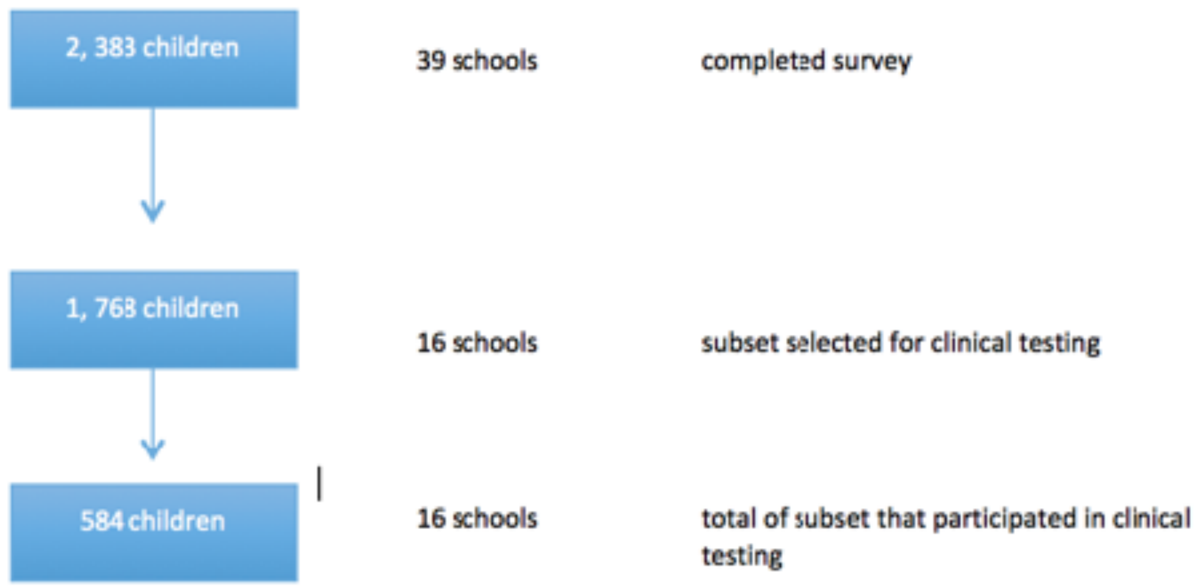


Figure 2: Selection for participants in clinical testing from survey participants.

tion testing, and skin prick testing. Clinical assessment was performed with a subset of students in grades 1-8 attending 16 selected schools. The schools for clinical assessment were chosen based on school participation numbers in the survey. This allowed for maximum efficiencies and reduction of cost. Of the 1768 students from the 16 schools selected for clinical testing, 584 agreed to participate in the clinical study. (47) This is presented in Figure 2.

3.2.3 Study protocol

A combination of methods for data collection was used for this study. These included a Questionnaire Survey Instrument and the aforementioned clinical measures.

3.2.3.1 Questionnaire

The questionnaires evaluated personal and contextual factors of importance to respiratory health and asthma. Personal factors included socio-demographic characteristics, smoking exposure, family and personal health history, and health behaviours. Contextual factors included social factors such as home environment, health behaviours and family factors. The questionnaire also included items describing farm type and types of farm activities performed on a regular basis.

The questionnaire provided structured and organized questions to limit bias. The questionnaire was based on: 1) the International Study of Asthma and Allergies in Childhood Study (ISAAC) questionnaire; (25, 29, 30, 47) 2) the American Thoracic Society's 1979 Children's Respiratory Disease Questionnaire (47, 48) (ATS); 3) the self-administered questionnaires in the Student Lung Health study; (47) 4) questionnaires used in previous lung health studies of Saskatchewan. (26, 27, 47)

3.2.3.2 Clinical Measures

A subset of children was invited to take part in clinical testing which included anthropometric measures, pulmonary function testing, and allergy skin prick testing.

Anthropometric Measures. Each participant had measurements of height, weight, and abdominal girth taken. These measures were taken objectively as part of the data required to generate normal values for the children in terms of the pulmonary function testing. Height was measured against the wall using a fixed measuring tape with the subjects standing in socks on a hard floor. Weight was measured using a calibrated spring scale with the subjects in socks and dressed in normal indoor clothing. From these measurements, body mass index (BMI) was calculated based on the equation:

[BMI = weight (kg)/ height $(m)^2$].

Abdominal girth was measured using a measuring tape kept parallel to the floor around the subject's waist, ensuring the tape was not twisted.

Pulmonary Function Testing. Pulmonary function was assessed through spirometry using the forced expiratory maneuver. A dry-rolling seal spirometer was used to conduct the testing. Pulmonary function measurements were taken according to the standards of the American Thoracic Society. (48) Children completed the testing while seated and wearing a nose clip. A minimum of three maneuvers were attempted to a maximum of seven. The calibration of the spirometer was performed daily prior to testing using a 3 L syringe as well as if there was a temperature change of greater than or equal to two degrees (2 ^{o}C).

The following measures were obtained:

1) Forced expired volume in one second (FEV 1)
2) Forced vital capacity (FVC)
3) FEV 1/ FVC x 100
4) Maximum mid-expiratory flow rate (FEF $_{25\text{-}75}$)

The exclusion criteria for pulmonary function testing included: recent cough or cold, use of short-acting asthma inhaler within the last two hours, recent use of an allergy pill or cough syrup or headache on the day of the pulmonary function testing. Further exclusion was considered following a brief questionnaire administered by the technician prior to the pulmonary function testing. It included questions on personal smoking on the day of testing and past medical health conditions that may be contraindications to pulmonary function testing. Other contraindications included: any recent surgery (within past 3 months), recent history of head, chest or abdominal injury, history of pneumothorax, cough with blood, heart problems (congenital or otherwise), hypertension (as reported by parent), contagious infection (flu, tuberculosis, norovirus, or pneumonia) or confusion, or inability to understand instructions to perform the test.

3.3 Statistical Analysis and Sample Size

3.3.1 Statistical analysis

The statistical analysis was completed using SPSS. Initially, descriptive analyses were completed for each question using frequencies and proportions for categorical variables and means with standard deviations for continuous variables. The descriptive analyses were completed using the data collected from the surveys and clinical measures. Following this, to adjust for potential confounding, multiple regression models were fitted using linear regression for continuous outcomes (e.g. lung function measures) and logistic regression for binary outcomes.

For this thesis's analysis, the analyses will include Grade 1 - 8 children with completed lung function data. In all analyses considering lung function, associations will be controlled for a minimum of age, sex, and height.

3.3.2 Statistical Power and Sample Size Requirements

For this study, a fixed population was available from the Saskatchewan Rural Health Study. To ensure an adequate population size for this thesis to detect the desired effect size to be measured, power calculations were completed. Sample size and power calculations were performed using GPower 3.1 software.

Pulmonary function questions were analyzed based on the data available for clinical testing. This sample size consisted of 584 children; 262 farm-dwelling children and 318 non-farm dwelling children. Based on a medium effect size of 0.5, a two tailed test, alpha value of 0.05, and a beta value of 0.2 (power=80%), a minimum sample size of 130 would be required. This sample size was available for the thesis. As seen in Figure 1, with 580 participants we would have a power of approximately 99%. To maintain 80% power, we could have an effect size as small as approximately 0.24. This would represent a small effect size. Given these calculations, the sample size available is more than adequate to detect the desired effect size and complete the analyses for this thesis. This is demonstrated in Figure 3.

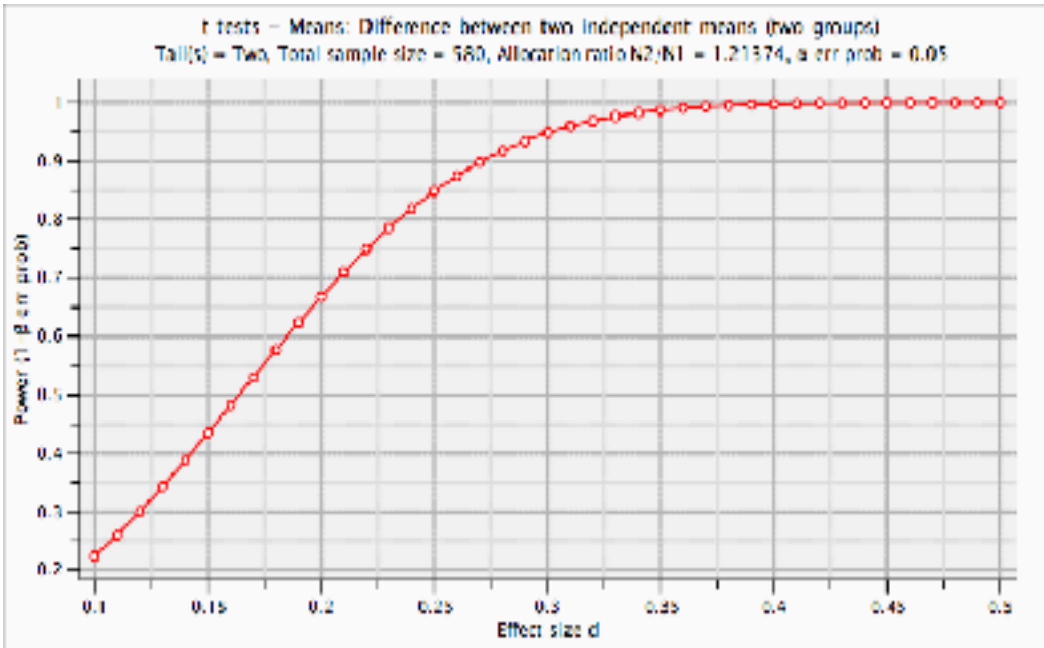


Figure 3: Plot of Power (y-axis) versus Effect size (x-axis

3.4 <u>Preliminary descriptive results</u>

3.4.1 Population Characteristics

A total of 2383 children completed the survey questionnaire. The participation rate was 42%. Of these completed surveys, 124 were excluded due to missing data. The final questionnaire sample size was 2259 participants. Of these, a subset was selected to participate in clinical testing. The final sample size was 584 for the clinical testing. Of this final sample, 568 had complete data for use in analysis.

3.4.2 Study Population

The study population characteristics are outlined in Table 3.1 (This table is repeated in Chapter 4 as Table 1 since it is part of the manuscript) and includes a comparison of those who did and who did not take part in the clinical testing based on the survey responses. A comparison of those who participated in clinical testing versus those who did not revealed that the prevalence of asthma between the two groups was similar. However, those who participated compared to those who did not included a higher proportion who were breastfed, Caucasian, had a higher level of paternal education, had a history of paternal asthma history, had a history of maternal asthma history, and attended daycare. Those included were also more likely to have reported a musty smell of mold/mildew in home, visited a farm regularly, and participated in farming exposures more regularly compared to those who did not participate in clinical testing.

Table 3.1: Descriptive Statistics of the study population comparing those who were included in lung function testing to those who were excluded

Variables	Included in Analysis (N = 568) (n = %)	Excluded from the Analysis (N = 1288) (n = %)	P value
Sex			
Female	270 (47.5)	658 (51.1)	0.158
Male	298 (52.5)	630 (48.9)	
Mean Age, years (SD)	9.59 (2.2)	10.35 (2.4)	<0.001
Ethnicity			
Caucasian	507 (91)	1083 (85.6)	0.001
Non-Caucasian	50 (9)	182 (14.4)	
Maternal Education			
High school or less	176 (87.1)	405 (86)	0.693
Any post-secondary Education	26 (12.9)	66 (14)	
Paternal Education			
High school or less	198 (70)	511 (76.7)	0.028
Any post-secondary education	85 (30)	155 (23.3)	
Hx of Early childhood illness			
Yes	147 (25.9)	347 (26.9)	0.634
No	421 (74.1)	941 (73.1)	
Asthma Status			
Ever Asthma	87 (15.5)	184 (14.4)	0.553
No Asthma	474 (84.5)	1090 (85.6)	
Children breastfed			
Yes	465 (82.4)	973 (76.7)	0.006
No	99 (17.6)	296 (23.3)	
Maternal history of Asthma			
Yes	47 (8.6)	112 (9.2)	0.674
No	502 (91.4)	1108 (90.8)	
Paternal history of Asthma			
Yes	54 (10.4)	87 (7.6)	0.051
No	464 (89.6)	1065 (92.4)	

Maternal History of allergic diseases Yes No	 167 (30.4) 383 (69.6)	 316 (25.9) 904 (74.1)	0.051
Paternal History of allergic diseases Yes No	 124 (23.9) 394 (76.1)	 276 (24) 876 (76)	0.993
Mother Smoking Ever Smoke Never Smoke	 217 (38.4) 348 (61.6)	 559 (43.8) 718 (56.2)	0.031
Mom Currently Smoking Yes No	 113 (20) 451 (80)	 264 (20.7) 1010 (79.3)	0.737
Father Smoking Ever Smoke Never Smoke	 250 (44.3) 314 (55.7)	 594 (46.6) 680 (53.4)	0.362
Dad Currently Smoking Yes No	 157 (27.9) 406 (72.1)	 319 (25.1) 951 (74.9)	0.212
Mother Smoking during pregnancy Yes No	 32 (6.8) 438 (93.2)	 78 (7.3) 935 (92.7)	0.711
Daycare Attendance Yes No	 325 (57.8) 237 (42.2)	 672 (52.7) 603 (47.3)	0.042
Cat in the home Yes No	 52 (9.8) 477 (90.2)	 131 (11) 1065 (89)	0.485
Presence of musty smell of mold/mildew in the home Yes No	 127 (23) 424 (77)	 217 (17.5) 1026 (82.5)	0.006
Presence of mold/mildew in the home Yes No	 113 (19) 450 (79.9)	 238 (18.6) 1042 (81.4)	0.457

House heating type			
Natural gas	422 (74.6)	921 (72.3)	0.312
Other	144 (25.4)	353 (27.7)	
Air-conditioning in the home			
Yes	277 (50.8)	628 (51.9)	0.689
No	286 (49.2)	583 (48.1)	
Air filter in the home			
Yes	217 (41.7)	537 (46.7)	0.061
No	303 (58.3)	614 (67)	
Humidifier in the home			
Yes	138 (26.6)	296 (26)	0.796
No	381 (73.4)	843 (74)	
Dehumidifier in the home			
Yes	243 (45.5)	484 (41.2)	0.095
No	291 (54.5)	691 (58.8)	
Presence of wood fireplace in the home			
Yes	83 (16.1)	224 (19.5)	0.091
No	434 (83.9)	923 (80.5)	
Home location			
Farm	308 (54.5)	726 (57.1)	0.299
Non-farm	257 (45.5)	545 (42.9)	
Farm type			
Livestock farm	124 (77.5)	91 (24.9)	0.549
Non livestock farm	36 (22.5)	274 (75.1)	
Mom lived on farm while pregnant			
Yes	179 (31.9)	403 (31.6)	0.901
No	383 (68.1)	874 (68.4)	
Visited a farm			
Regularly	333 (66.2)	436 (39.5)	0.030
Never/Not regularly	170 (33.8)	669 (60.5)	
Consumption of unpasteurized milk in first year of life			
Yes	15 (2.7)	39 (3.1)	0.631
No	544 (97.3)	1220 (96.9)	

Lived on farm in first year of life Yes No	 173 (30.6) 392 (69.4)	 397 (30.9) 886 (69.1)	 0.890
(Farming Exposure Variables)			
Haying or moving or playing with hay bales Regularly Not Regularly	 132 (23.7) 426 (76.3)	 249 (19.7) 1016 (80.3)	 0.055
Feeding livestock Regularly Not Regularly	 148 (26.6) 409 (73.4)	 274 (21.7) 987 (78.3)	 0.024
Cleaning or playing in barns Regularly Not Regularly	 128 (22.9) 430 (77.1)	 210 (16.6) 1054 (83.4)	 0.001
Emptying or filling grain bins Regularly Not Regularly	 46 (8.2) 512 (91.8)	 82 (6.5) 1178 (93.5)	 0.182
Cleaning or playing in pens and corrals Regularly Not Regularly	 120 (21.5) 437 (78.5)	 195 (15.5) 1066 (84.5)	 0.002
Riding horses Regularly Not Regularly	 48 (8.6) 510 (91.4)	 149 (11.8) 1113 (88.2)	 0.042

3.4.3 Comparison of characteristics between farm and non-farm children

The farm and non-farm study populations are compared in Table 3.2. In the table, a comparison of farm versus non-farm dwelling children revealed that the personal and environmental characteristics of both groups were similar. However, farm-dwelling children included a higher proportion who were Caucasian, had more childhood pneumonia, more natural gas heating in home, more fireplace in home, and more likely to report presence of musty smell of mold/mildew in the home. Non-farm dwelling children were also more likely to report a history of mom being an ever-smoker, current smoker or smoking during pregnancy, a history of father being an ever-smoker or current smoker. The non-farm dwelling children also had a higher proportion of who attended daycare, had an air-conditioner in the home, and had a cat or dog in the home, compared to farm-dwelling children.

Table 3.2: Personal and Environmental Characteristics among those who took part in Lung Function Testing by location of residence

Variables	Total Population (n=565)		Farm Children (n=257)		Non-Farm Children (n=308)		P value
Sex							
Female	269	(52.4%)	120	(44.6%)	149	(55.4%)	0.690
Male	296	(47.6%)	137	(53.4%)	159	(51.6%)	
Mean Height, cm (SD)	142.42	(15.09)	143.11	(15.27)	141.82	(14.99)	0.448
Mean Weight, kg (SD)	39.14	(13.35)	39.39	(14.39)	39.43	(15.19)	0.554
Mean Age, years (SD)	9.59	(2.21)	9.70	(2.24)	9.49	(2.20)	0.665
Ethnicity							
Caucasian	505	(91.2%)	240	(94.1%)	265	(88.6%)	0.023
Not Caucasian	49	(8.8%)	15	(5.9%)	34	(11.4%)	
Firstborn child							
Yes	334	(60.2%)	164	(64.6%)	170	(56.5%)	0.052
No	221	(39.8%)	90	(35.4%)	131	(43.5%)	
Hx of Childhood Illness							
Yes	147	(26%)	75	(29.2%)	72	(23.4%)	0.117
No	418	(74%)	182	(70.8%)	236	(76.6%)	
Bronchitis							
Yes	81	(15%)	38	(15.4%)	43	(14.6%)	0.777
No	460	(85%)	208	(84.6%)	252	(85.4%)	

Pneumonia							
Yes	48	(8.9%)	29	(11.7%)	19	(6.5%)	0.034
No	493	(91.1%)	219	(88.3%)	274	(93.5%)	
Sinus trouble							
Yes	46	(8.5%)	20	(8.1%)	26	(8.8%)	0.786
No	496	(91.5%)	226	(91.9%)	270	(91.2%)	
Croup							
Yes	74	(13.7%)	36	(14.9%)	38	(12.8%)	0.475
No	466	(86.3%)	206	(85.1%)	260	(55.2%)	
Children breast-fed							
Yes	465	(82.9%)	220	(86.3%)	245	(80.1%)	0.052
No	96	(17.1%)	35	(13.7%)	61	(19.1%)	
Overweight	119	(21.1%)	45	(17.5%)	74	(24 %)	0.059
Not overweight	446	(78.9%)	212	(82.5%)	234	(76 %)	
Obese	24	(4.2%)	7	(2.7%)	17	(5.5%)	0.101
Not Obese	541	(95.8%)	250	(97.3%)	291	(94.5%)	
Obesity Status							
Underweight	28	(5%)	14	(5.4%)	14	(4.5%)	
Not Overweight	391	(69.2%)	185	(72 %)	206	(66.9%)	
or Obese	109	(19.3%)	47	(18.3%)	62	(20.1%)	0.194
Obese	37	(6.5%)	11	(4.3%)	26	(8.4%)	
Maternal Hx of Allergy							
Yes	166	(30.3%)	78	(31.1%)	88	(29.7%)	0.733
No	381	(69.7%)	173	(68.9%)	208	(70.3%)	
Maternal Hx of Asthma							
Yes	46	(8.4%)	17	(6.8%)	29	(9.8%)	0.200
No	500	(91.6%)	234	(93.2%)	266	(90.2%)	
Paternal Hx of Allergy							
Yes	123	(23.9%)	56	(23.2%)	67	(24.5%)	0.747
No	392	(76.1%)	185	(76.8%)	207	(75.5%)	

Paternal Hx of Asthma							
Yes	462	(89.7%)	214	(88.8%)	248	(90.5%)	0.523
No	53	(10.3%)	27	(11.2%)	26	(9.5%)	
Mother Smoking							
Ever Smoke	214	(38.1%)	68	(26.6%)	146	(47.7%)	<0.001
Never Smoke	348	(61.9%)	188	(73.4%)	160	(52.3%)	
Mother Currently Smoking							
Yes	256	(45.6%)	35	(13.7%)	77	(25.2%)	0.001
No	305	(54.5%)	221	(86.3%)	228	(74.8%)	
Father Smoking							
Ever Smoke	249	(44.4%)	84	(32.9%)	165	(53.9%)	<0.001
Never Smoke	312	(55.6%)	171	(67.1%)	141	(46.1%)	
Father Currently Smoking							
Yes	156	(27.9%)	53	(20.6%)	103	(34%)	<0.001
No	404	(72.1%)	204	(79.4%)	200	(66%)	
Mother Smoking during pregnancy							
Yes	32	(6.8%)	9	(4.1%)	23	(9.3%)	0.025
No	436	(93.2%)	212	(95.9%)	224	(90.7%)	
Daycare Atten-dance							
Yes	323	(57.8%)	126	(49.2%)	197	(65%)	<0.001
No	236	(42.2%)	130	(50.8%)	106	(35%)	
Cat in the home							
Yes	206	(36.5%)	79	(30.7%)	127	(61.7%)	0.010
No	359	(63.5%)	178	(69.3%)	181	(41.2%)	
Dog in the home							
Yes	237	(41.9%)	90	(35 %)	147	(47.7%)	0.002
No	328	(58.1%)	167	(65 %)	161	(52.3%)	
Presence of musty smell of mold/mildew in the home							
Yes	112	(20 %)	67	(26.2%)	45	(14.8%)	0.001
No	448	(80 %)	189	(73.8%)	259	(85.2%)	

Presence of mold/mildew in the home							
Yes	127	(23.2%)	61	(24.3%)	66	(22.2%)	0.565
No	421	(76.8%)	190	(75.7%)	231	(77.8%)	
House heating type							
Natural gas	144	(25.6%)	127	(49.8%)	17	(5.5%)	<0.001
Other	419	(74.4%)	128	(50.2%)	291	(94.5%)	
Air-conditioning in the home							
Yes	275	(50.7%)	96	(40 %)	179	(59.3%)	<0.001
No	267	(49.3%)	144	(53.9%)	123	(46.1%)	
Air filter in the home							
Yes	216	(41.7%)	96	(42.3%)	120	(41.2%)	0.809
No	302	(58.3%)	131	(57.7%)	171	(58.8%)	
Humidifier in the home							
Yes	137	(26.5%)	67	(29 %)	70	(24.5%)	0.246
No	380	(73.5%)	164	(71 %)	216	(75.5%)	
Dehumidifier in the home							
Yes	242	(45.5%)	113	(47.9%)	129	(43.6%)	0.322
No	290	(54.5%)	123	(52.1%)	167	(56.4%)	
Presence of wood fireplace in the home							
Yes	83	(16.1%)	62	(26.8%)	21	(7.4%)	<0.001
No	432	(83.9%)	169	(73.2%)	263	(92.6%)	

3.4.4 Pulmonary Function levels

The overall study population had good pulmonary function levels. Adjusted associations between the measures of lung function and independent variables of interest used as main effects in the models for the thesis are presented in Table 3.3. Statistically higher FEV1 was seen with mother not currently smoking, absence of cat in home, absence of musty smell/mold in home, and presence of humidifier in home (Table 3.3). Children with negative maternal allergy history, regularly emptying or filling grain bins, and absence of cat in home had higher FVC than their respective comparison groups (Table 3). Higher FEV1/FVC was seen with no previous asthma diagnosis, previous childhood illness history, no previous bronchitis history, no previous pneumonia history, positive maternal allergy history, mother never smoking, mother not currently smoking, absence of mold/mildew in home, house heating type other than natural gas, and absence of wood fireplace in home (Table 2).

<u>Table 3.3:</u> Adjusted associations between the Main Effects and Lung Function Outcomes*

Primary Variable	FEV			FVC			FEV/FVC			FEF		
	→	S.E.	p-value	→	S.E.	p-value	→	S.E.	p-value	→	S.E.	p-value
Child Age	0.014	0.013	0.282	0.025	0.015	0.094	-0.005	0.003	0.125	0.010	0.027	0.702
Sex	-0.079	0.027	0.003	-0.166	0.032	<0.005	0.015	0.005	0.025	0.101	0.057	0.077
Height	0.037	0.002	<0.005	0.045	0.002	<0.005	0.000	0.000	0.500	0.035	0.004	< 0.005
Asthma Diagnosis	-0.038	0.034	0.332	0.012	0.047	0.789	-0.017	0.009	0.077	-0.161	0.083	0.054
Childhood Illness	-0.012	0.032	0.706	0.011	0.038	0.762	-0.015	0.008	0.048	-0.082	0.067	0.222
Pat Hx of Asthma	-0.033	0.044	0.455	0.004	0.052	0.943	-0.010	0.011	0.360	-0.176	0.093	0.060
Mat Hx of Asthma	-0.071	0.060	0.236	-0.136	0.070	0.054	0.015	0.014	0.297	-0.025	0.125	0.844
Mat Hx of Allergy	0.025	0.032	0.422	0.071	0.037	0.057	-0.013	0.008	0.082	-0.037	0.067	0.581
Mat Ex Smoker	0.181	0.299	0.546	0.085	0.354	0.809	-0.012	0.071	0.869	0.327	0.630	0.604
Mat Current Smoker	-0.194	0.294	0.516	-0.096	0.354	0.787	0.006	0.071	0.930	-0.355	0.630	0.573
Daycare	0.042	0.027	0.120	0.043	0.032	0.182	-0.001	0.007	0.932	0.027	0.057	0.638

Cat in Home	-0.053	0.029	0.068	-0.054	0.034	0.120	-0.008	0.007	0.227	-0.094	0.061	0.124
Signs of Mold Smell	-0.053	0.036	0.138	0.007	0.042	0.869	-0.018	0.009	0.036	-0.201	0.076	0.008
Mold/ Mildew	-0.045	0.035	0.198	-0.027	0.041	0.511	0.000	0.008	0.962	-0.081	0.074	0.274
Wood Fire-place	0.025	0.039	0.523	0.048	0.047	0.301	-0.019	0.009	0.134	0.015	0.083	0.857
Air Filter	-0.002	0.028	0.949	0.013	0.033	0.694	-0.007	0.007	0.299	-0.050	0.059	0.397
House-heating type	-0.019	0.031	0.541	-0.020	0.036	0.591	-0.008	0.007	0.278	-0.009	0.065	0.895
Humid-ifier	0.043	0.032	0.177	0.048	0.038	0.207	-0.004	0.008	0.562	0.036	0.067	0.595

*Adjusted for all variables in the table

CHAPTER FOUR:

LUNG FUNCTION IN RELATION TO FARM DWELLING AND FARMING ACTIVITIES IN RURAL DWELLING CHILDREN

4.1 Abstract:

Background:

Asthma severity indicators such as lower lung function and their risk factors are understudied in farming and non-farming populations. Pulmonary function testing is a consistent and valid measure to diagnose asthma and evaluate its severity. The objective of this study was to evaluate the relationship between farming exposures and pulmonary function in a rural pediatric population.

Methods:

For this study, data from the Saskatchewan Rural Health Study (SRHS) was used. SRHS is a population-based study, conducted in 2011, evaluating respiratory health of rural dwelling children and adults in the province of Saskatchewan, Canada. The SRHS is designed as a cohort study. However, data used for this analysis is from the baseline data cross-sectional study. The initial data collected included a parent-completed survey questionnaire answered on behalf of the child. From this study sample, a subset of children (6-14 years old) was selected to participate in clinical testing, which included anthropometric measures and pulmonary function testing (PFT) using spirometry (n=584). This subset was selected from schools bases on

participation numbers in the survey. PFTs followed ATS criteria and all statistical analyses were controlled for child age, sex, and height.

Results:

Among children participating in clinical testing, 47.5% were female and 54.5% lived on a farm. Of those living on farms, 77.5% were livestock farms. The mean percent predicted value (PPV) for forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) among those living on the farm were 104.8% and 105.4%, respectively while mean PPV for FEV_1 and FVC among non-farm dwellers were 102.7% and 101.4%, respectively. After adjustment for potential confounders using linear regression, higher FEV_1 (β = 0.079, S.E= 0.033, p=0.03) and FVC (β = 0.110, S.E= 0.039, p=0.006) was associated with living on a farm, while there was a trend towards lower FEV_1/FVC ratio (β = -0.013, S.E= 0.008, p=0.09). Higher FVC and lower FEV_1/FVC ratio were also seen with children who regularly emptied grain bins ($p<0.05$). Of note, trends towards a higher FEV_1 (p=0.14) and FVC (p=0.08) were also seen with children who lived on a farm in the first year of life. As the majority of the population was Caucasian, (91%), the results were not race-corrected.

Conclusion:

While mild obstruction was seen for children living on a farm, higher FEV1 and FVC were also observed suggesting, that there are differences in lung function between children who live on a farm and those who do not. Despite a higher FEV_1 and FVC among farm dwellers and a trend towards a higher FEV1 and FVC was also seen with children who lived on a farm in the first year of life, the FEV1/FVC ratio was lower compared to non-farm dwellers, suggesting that there are differences in lung function seen in farm dwelling children.

4.2 **Background:**

In Canada, asthma is a common, resource intensive disease costing millions of dollars annually and a leading cause of school absenteeism.(1-5) Despite this, recent literature shows that asthma severity and morbidity are underestimated and better understanding is needed to improve asthma prevention and treatment. (2, 6-8) Pulmonary function testing is an objective measure used to help diagnose asthma and evaluate its severity.(6,9,10) There is a lack of clinical information in the lung health of rural populations, specifically of lung function assessment and asthma severity and morbidity, which is distressing since rural dwellers can have health care access issues. (7, 11-16) An investigation of lung function in rural dwellers will be important from a health care and etiologic perspective since without a strong understanding of pulmonary function in this population, it is difficult to understand diagnostic and severity issues, especially related to asthma. (6, 9, 10, 19, 20, 43-45)

The objective of this analysis was to investigate pulmonary function in a rural pediatric Canadian population. We considered the following research questions: (1) What are levels of pulmonary function in a rural population of children?; (2) Are there differences in pulmonary function between farm and non-farm dwelling children? and; (3) Are certain types of farming activities associated with pulmonary function?

4.3 <u>Materials and Methods:</u>

4.3.1 Study design and population

Data from the Saskatchewan Rural Health Study (SRHS) was used for this study, the methods of which have been described (28,34,42,47). Briefly, SRHS is a large cohort study with adult and child components evaluating health of rural dwelling residents of Saskatchewan with primary focus on respiratory health. Data was collected from residents in four rural quadrants of Saskatchewan. Data used for analysis was from a cross-sectional survey and clinical assessments conducted at baseline.

Rural was defined as people living in municipalities and towns with a population of 10,000 or less and residing outside the commuting zone of urban centers, at least 60 kilometres from an urban center.(47) Purposeful sampling was done using a multistage, stratified sampling strategy. Initial stratification consisted of dividing southern Saskatchewan into four quadrants (Northwest, Northeast, Southwest and Southeast), to appropriately represent Saskatchewan's varied farming types and to find populations living outside the commuting area of larger centers. (47)

School divisions with schools in rural municipalities selected for the adult study (47) were approached. The initial survey for the child cohort consisted of rural dwelling children aged 6 – 18 years. Questionnaires and consent forms for clinical testing were distributed through schools to the parents of children attending that school in January 2011. Parents were asked to complete and return surveys and consent for pulmonary studies. These were collected by members of the research team.

Overall, 39 out of 43 schools invited to participate took part. From these schools, 2383 children participated in the baseline survey study (participation rate: 42%). A subset of this group was invited to participate in clinical testing including anthropometric measures, pulmonary function testing, and skin prick testing. Inclusion criteria for clinical testing was that the student must be in Grades 1-8 and attend one of 16 selected schools. Schools for clinical assessment were chosen based on school survey participation numbers to allow maximum efficiency and reduction of cost. The final inclusion criteria was based on a question from the survey. Participants were asked, 'Would you be willing to be contacted about having breathing and/or allergy tests at a nearby location?' Those who responded positively to this question and who met the other two criteria were invited to participate in a clinical assessment.(47) Of 1768 eligible students from selected schools, 584 participated in the clinical study (47). Clinical testing was performed by 580 students with complete lung function data available for 568 of these participating students. Clinical testing was completed in February to April 2011.

The University of Saskatchewan Biomedical Research Ethics Board and local school boards approved the study. Parents and children completed consent and assent forms for clinical assessment, respectively, prior to participation. Children were allowed to refuse testing at any time before and during clinical procedures.

4.4 Study protocol

4.4.1 Questionnaire

Questionnaires evaluated personal, environmental, and contextual factors important to respiratory health. The questionnaire was based on: 1) International

Study of Asthma and Allergies in Childhood Study (ISAAC) questionnaire;(21-23, 46) 2) American Thoracic Society's 1979 Children's Respiratory Disease Questionnaire (ATS)(48); 3) self-administered questionnaires in the Student Lung Health study(49); 4) questionnaires used in previous Saskatchewan lung health studies(43,44).

Independent Variables:

Asthma diagnosis was defined as a physician's report of diagnosis based on the question "Has this child ever been diagnosed as having asthma by a doctor?" Farming exposure variables were described in the study by Barry et al.(25). Home location was defined as farm if it was reported the child lived on a "farm" or "acreage" and small town if the child reported living "in town". Farming exposure variables included: Haying or moving or playing with hay bales; Feeding livestock; Cleaning or playing in barns; Emptying or filling grain bins; Cleaning or playing in pens and corrals; and riding horses. For each, amount of activity was based on the question: "In the past 12 months, on average, how often has this child spent 1 hour near or in the following activities" with response options of "Everyday; At least once a week; At least once a month; Less than once a month; and Never". These were categorized into binary variables (regular vs irregular activity) where regular included every day, weekly and monthly.(25) Livestock farming was defined as farm where any of the following commodities were produced for sale; cattle (beef), cattle (dairy), pigs, or poultry.

4.3.2.2 Anthropometric and lung function outcomes:

Each participant had objective measurements of height and weight taken. (47) Height was measured against the wall using a fixed measuring tape with subjects standing in socks on a hard floor. Weight was measured using a calibrated spring scale with subjects in socks and dressed in normal indoor clothing. Body mass index (BMI) was calculated based on the equation [BMI = weight (kg)/ height $(m)^2$].(47)

Outcome variables - Lung Function Measures:

Pulmonary function was assessed through spirometry using the forced expiratory maneuver. A *Sensormedics* (Anaheim, CA) dry-rolling seal spirometer was used for testing. Pulmonary function measurements followed American Thoracic Society standards. (50) Children completed testing while seated wearing a nose clip. A minimum of three maneuvers were attempted to a maximum of seven. The following measures were obtained: Forced expired volume in one second (FEV_1); Forced vital capacity (FVC); FEV_1/FVC ratio (FEV_1/ FVC x 100); and Forced Expiratory Flow between 25-75% of FVC (FEF_{25-75}).

4.5 <u>Statistical Analysis:</u>

Statistical analysis was completed using SPSS and used data collected from surveys and clinical measures. Descriptive analyses were completed for each question. We compared those who participated in pulmonary function testing component of the study to those who did not. Chi-squared test was used for categorical variables and independent samples t-test for continuous variables.

Pulmonary function comparisons between farm and non-farm populations were completed using absolute and percent predicted values (Knudsen (49)). For absolute comparisons, Analysis of Covariance (ANCOVA) was used. As pulmonary function varies with age, sex, and height (47), statistical analysis was adjusted for these and other potential confounders, which included the following: age, sex, height, childhood illness, paternal history of asthma, maternal history of asthma, maternal history of allergy, mother ex-smoker, mother current smoker, daycare attendance, presence of cat in the home, signs of mold in the home, mold/mildew present in the home, wood fireplace in the home, air filter in the home, humidifier in the home. Pulmonary function and its analyses were not race corrected since the majority of the population (91%) was Caucasian. When comparing percent predicted pulmonary function values between farm and non-farm populations, comparisons were made using independent-sample t-tests. In all analyses, each pulmonary function measure was considered independently of the others.

We then investigated associations between pulmonary function and selected rural exposure variables based on clinical and statistical importance. The dependent variable was the absolute measure of pulmonary function. Independent variables of primary interest included home location (farm or non-farm) and farming exposure variables. These were evaluated separately to avoid collinearity. Additional independent variables were selected to the final model based on the protocol of Hosmer et al. (49) where variables in the multivariable model were included based on statistical significance ($p<0.20$), importance from the literature, and the effect a variable has on other variables in model after its removal. Once the final main effects model was fitted, we assessed interaction between sex and farm variables and asthma status with the farm variables using the likelihood ratio test to test the addition of an interaction term to the main effects model. These interaction terms were selected a priori based on the literature and included farming exposures with sex and farming exposures with asthma status.(20,28,46) If interaction was present, stratified analyses were presented.

4.6 <u>Results:</u>

Among those who participated, a higher proportion were breastfed, Caucasian, had a higher level of paternal education, had a history of paternal asthma history, had a history of maternal asthma history, attended daycare, and reported a musty smell of mold/mildew in home, visited a farm regularly, and participated in farming exposures more regularly compared to those who did not participate in clinical testing (Tables 1 and 2).

Overall, the study population had normal lung function. The average percent predicted FEV_1 was 102.7% (non-farm) and 104.8% (farm) and overall average percent predicted FVC was 101.4% (non-farm) and 105.4% (farm). Average FEV_1/FVC ratio was 88% (non-farm) and 86% (farm).

Table 3 presents pulmonary function after adjustments for asthma status, farming activities and home location variables. There was no statistically significant difference in pulmonary function based on home location. Among those who participated, higher FEV_1/FVC was seen in patients without asthma (p=0.005) compared to those with asthma. Higher FVC was seen with emptying and filling grain bins when compared to not doing this activity regularly (p= 0.001). Although not statistically significant, lower FEV_1/FVC ratio was seen with emptying or filling grain bins regularly (p=0.070) while a higher ratio was observed for children who lived on livestock farms (p=0.070).

Table 4 presents pulmonary function after adjustments for home location, farming activities and early farming exposures. Higher FEV_1 and FVC were seen with living on farm while higher FVC was seen with emptying and filling grain bins regularly. On average, children who had a mother who lived on the farm while pregnant had a higher FEV1.

When considering interaction between sex and farming exposures, no statistically significant interaction was found. There was, however, interaction between asthma status and farming activities and farming exposures. Stratified results are presented in Figures 4. Higher FEV_1 and FVC were seen with living on farm among those without asthma. Lower FEV_1/FVC was seen with feeding livestock regularly among those without asthma. Higher FVC and lower FEV_1/FVC were also seen with emptying grain bins regularly among those without asthma.

4.7 <u>Discussion:</u>

We found differences in pulmonary function between farming and non-farming rural dwelling children. Several associations, however, were modified by asthma status where lower pulmonary function was seen with certain exposures among those without an asthma diagnosis, including not living on a farm, and regular farming exposures such as haying. No interaction was observed with sex. Overall, the population under study was healthy with normal pulmonary function based on percent predicted values.

Despite higher FEV_1 and FVC among farm dwelling children, FEV_1/FVC ratio was lower compared to non-farm dwelling children. Emptying grain bins regularly was associated with higher FEV_1 and FVC compared to not regularly participating. Certain early farm exposures have been shown to have inverse associations with asthma presence including: living on farm in first year of life, drinking unpasteurized milk in first year of life, and mother living on farm while pregnant.[28-33]

Certain types of farming and farming activities have also been shown to be protective against asthma including livestock farming and activities including livestock, riding horses, and cleaning or playing in pens/corrals.[28-33] Grain-farming activities were associated with higher rates of asthma. (28-33) Results from these previous studies considered presence of asthma as the outcome. We complement these earlier results by considering objective measures of pulmonary function as our outcome. In our study, emptying grain bins regularly was associated with higher FEV_1 and FVC. However, it has been associated with lower FEV_1 and FVC in the literature. (14,37-39) Higher FEV_1 and FVC may be representative of children's health who are participating in these chores. Children who are healthier or without respiratory disease are more likely to be active and participate in more demanding chores. There is evidence that higher FVC is seen in more athletic or active individuals. (50) This may be present with farm-dwelling children as they may be more active with physically demanding chores on the farm.

Interaction between various farming exposures and asthma status was observed. One may also expect that the presence or absence of an asthma diagnosis may influence types of activities in which children may be allowed to participate. Parents may elect to have their children with asthma avoid asthma triggers or strenuous activities. Despite these facts, trends towards higher FEV_1 and FVC were seen with living on farm in first year of life suggesting differences in pulmonary function seen in farm dwelling may not be purely due to reverse causality. Children with asthma may also experience differential reaction to certain exposures. (28,30) They may be more sensitive to pro-inflammatory effects due to hyper-responsive airways and inflammatory airway changes secondary to their asthma. (28,30,32,)

Early life farming exposures including drinking unpasteurized milk in first year of life was not associated with pulmonary function measures in our study. Mother living on farm while pregnant, however, was found to be significant for FEV_1. Early life farming exposures have been predictors of presence of asthma. They may not, however, be equally predictive pulmonary function.(9,10,28) This may be because of differential reaction to exposures and timing of exposure compared to timing of pulmonary function testing. They may lend to long term protective effects against asthma but not impact or influence asthma severity.

Environmental exposures differed between the farming and non-farming group. This included smoking. The estimated time of smoking exposure was assessed by survey questionnaire. There may be recall bias by the participants filling out the survey. Participants may underestimate or overestimate the length of smoking exposure. The smoking exposure may also precede the occurrence of asthma, or have come after. It would be difficult to truly ascertain the timing of smoking exposure compared to the time of onset of asthma. This may result in residual confounding of asthma and pulmonary function being more influenced by smoking exposure than can be evaluated.

With regards to potential limitations of the study, there may be selection bias. There were more children with parents with higher education or who had history of asthma or allergic disease among those included compared to those excluded from the study. This may select for children in healthier environments or influenced by healthier behaviours as modelled by parents. Given that the overall population of children is healthy, based on average lung function values, effects of this bias were likely limited. There is also the potential of confounding by the timing of exposures known to impact pulmonary function and respiratory health. The true exposure and its timing of factors like smoking are difficult to determine and may influence pulmonary function and asthma pathogenesis in the study population more than can be determined in this study. We also used a fixed population from the Saskatchewan Rural Health Cohort Study, which could present problems with statistical power. A power calculation was performed and confirmed the study population was adequate to see a moderate effect. In addition to this, we found statistically significant associations. There may also have been an issue with the subjective assessment of exposure do to its presence or absence being based on questionnaire report.

The study also has many strengths. The population was from the SRHS which sampled different rural quadrants of Saskatchewan. This allows for geographical variance within the study population and better representation of the rural population in Saskatchewan improving generalizability. Use of a validated and well-structured questionnaire allows for collection of significant and pertinent data. Using objective, clinical measures including pulmonary function testing also adds validity and strength to our research findings. Finally, Lung Association of Saskatchewan trained and certified staff were used for data collection. Also, the staff used were consistent across the project.

4.8 Conclusion:

Differences in lung function were seen between farm, non-farm dwelling children and certain farming activities. This research may serve as a launch point for further study of relationships between asthma, asthma severity and environment. Future work may include using pulmonary function as a measure to determine efficacy of asthma treatments and morbidity prevention strategies.

References :

1. Ismaila A, et al. Clinical, economic, and humanistic burden of asthma in Canada: a systemic review

    BMC Pulmonary Medicine 2013, 13:70 10.1186/1471-2466-13-70

2.Lung disease imposes major costs on Canada's Economy. The Conference Board of Canada, New Release. March 2012

3.Bahadori K,et al. Economic Burden of Asthma: Systematic Review. BMC Pulmonary Medicine 2009.

4.Sadatsafavi M, et al. Direct health care costs associated with asthma in British Columbia. Canadian Respiratory Journal. 2010 Mar-Apr; 17(2); 74-80.

5.Canadian Institute for Health Information. Respiratory Disease in Canada. Statistics Canada;2001.

6. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach, 2007.

7. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach, update 2010.

8.Stout J, et al. Classification of Asthma Severity in Children: The Contribution of Pulmonary Function Testing. Arch Pediatrics. 2006

9.Valet et al. High Asthma Prevalence and increased morbidity among rural children in Medicaid cohort. Annals of Allergy, Asthma, and Immunology. 2011

10.Chrischilles E, et al. Asthma prevalence and morbidity among rural Iowa school children. Journal of Allergy and Clinical Immunology 2004; 113:66–71.

11.Lawson, J., et al. Relationship between indoor environment and asthma and wheeze severity among rural children and adolescents. *Journal of Agromedicine* 2009;14(2):277-85.

12.Glover et al. Preventable Asthma Episodes Among Urban/Rural Children and Adolescents: A Comparative Study. Journal of Health Disparities Research and Practice. 2010

13.Douwes J, et al. Farm exposure in utero may protect against asthma, hay fever and eczema. Journal of European Respirology 2008; 32:603–611.

14.Ege MJ, et al. Not all farming environments protect against the development of asthma and wheeze in children. Journal of Allergy and Clinical Immunology 2007;119: 1140–1147.
15. Ernst P, Cormier Y. Relative scarcity of asthma and atopy among rural adolescents raised on a farm*. Am J Respir Crit Care Med* 2000; 161(5):1563-6.

16. Yawn BP, et al. Do rural and urban children have comparable asthma care utilization?*. J Rural Health* 2001; 17(1):32-9.

17. Rabe et al. Worldwide severity and control of asthma in children and adults: The global Asthma Insights and Reality Surveys. Journal of Allergy and Clinical Immunology. 2004

18. J. Lawson et al. Urban-rural differences in asthma prevalence among young people in Canada: the roles of health behaviours and obesity. Annals of Allergy, Asthma, and Immunology. 2011

19. R. Garner and D. Kohen. Changes in the prevalence of asthma in Canadian children. Statistics Canada Catalogue no. 82 – 003 – X Health Reports. June 2008 (Vol. 19 No. 2)

20. Bröms et al. Effect of degree of urbanisation on age and sex-specific asthma prevalence in Swedish preschool children. BMC Health. 2009

21. Asher, et al. International Study of Asthma and Allergies in Children (ISAAC): Rationale and Methods. Journal of European Respirology 1995. 8; 483 – 491

22.Weiland, et al. Phase II of the International Study of Asthma and Allergies in Children (ISAAC II): Rationale and Methods. Journal of European Respirology 2004. 24; 406-412

23.Asher et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in children. ISAAC Phases I and III repeat multi-country cross-sectional surveys. Lancet 2006. 368; 733-743

24.Asher M, et al. The International Study of Asthma and Allergies in Childhood (ISAAC).ISAAC Steering Committee. *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology* 1998;28:52.

25. Chrischilles E, et al. Asthma prevalence and morbidity among rural Iowa school children. Journal of Allergy and Clinical Immunology 2004; 113:66–71.

26. Kemp T, Pearce N, Crane J, Beasley R. Problems of measuring asthma prevalence*. Respirology* 1996;1(3):183-8

27. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach, update 2010.

28.Barry RJ, et al. Factors contributing to risks for pediatric asthma in rural Saskatchewan. Annals of Allergy, Asthma and Immunology 2012

29. Merchant J, et al. Asthma and Farm Exposures in a Cohort of Rural Iowa Children. (Keokuk Rural Study). Environ Health Perspect. Mar 2005; 113(3): 350-356

30.MacNeill SJ, et al. Asthma and allergies: is the farming environment (still) protective in Poland? The GABRIEL Advanced Studies. Allergy 2013; 68: 771–779

31.Midodzi WK, Rowe BH, Majaesic CM, Senthilselvan A. Reduced risk of physician-diagnosed asthma among children dwelling in a farming environment. *Respirology* 2007; 12(5):692-9.

32.Reidler et al. Allergic diseases and atopic sensitization in children related to farming and anthroposophic lifestyle – the PARSIFAL study. Allergy 2006; 61:414–421.

33.Farthing , et al. Farming Activities and Respiratory Health in School Age Children. 2007

34.Voter et al. Pulmonary Function Testing in Childhood Asthma. Immunology and Allergy Clinics of North America.

35. Wickens K, et al. Farm residence and exposures and the risk of allergic diseases in New Zealand children. Allergy 2002;57:1171–1179.

36.Radon K, et al. Farming exposure in childhood, exposure to markers of infections and the development of atopy in rural subjects. Clin Exp Allergy 2004; 34:1178–1183.

37.Remes ST, et al. Which factors explain the lower prevalence of atopy amongst farmers' children? Clin Exp Allergy 2003; 33:427–434.

38.Viinanen A, et al. The protective effect of rural living against atopy in Mongolia. Allergy 2007; 62:272–280.

39.Remes ST, et al. Does heredity modify the association between farming and allergy in children? Acta Paediatr 2002; 91:1163–1169.

40.Downs SH, et al. Having lived on a farm and protection against allergic diseases in Australia. Clin Exp Allergy 2001; 31:570–575.

41. Dimich-Ward H, Chow Y, Chung J, Trask C. Contact with livestock--a protective effect against allergies and asthma? *Clin Exp Allergy* 2006; 36(9):1122-9

42.Chu et al. Prevalence and determinants of atopy and allergic diseases among school-age children in rural Saskatchewan, Canada. Annals of Allergy, Asthma and Immunology 2014: 113: 430 – 439

43.Lawson, J., et al. Regional variations in risk factors for asthma in school children. *Can Respir J* 2005; 12(6):321-6.

44.Rennie, D., et al. Differences in respiratory symptoms and pulmonary function in children in 2 Saskatchewan communities. *Annals of Allergy and Asthma Immunology* 2004; 92(1):52-9.

45.Lawson, J., et al. Occurrence of new onset wheeze in a 3-year follow-up study of schoolchildren. *Ann Allergy Asthma Immunol* 2007;99(6):502-8.

46. British Thoracic Society Asthma Guidelines. 2012

47.Pahwa P, et al. Saskatchewan Rural Health Study. BMC Research Notes 2012.

48. Ferris et al. ATS Epidemiology development. Thorax. 1978

49. Knudson et al. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983;127(6):725

50. Fuster V., et al Physical Activity Related to Forced Vital Capacity and Strength Performance in a Sample of Young Males and Females. Coll. Antropol. 2008 1: 53-60

Table 1: Descriptive Statistics of the study population comparing those who were included in lung function testing to those who were excluded

Variables	Included in Analysis (N = 568) n (%)	Excluded from the Analysis (N = 1288) n (%)	P value
Sex			
Female	270 (47.5)	658 (51.1)	0.158
Male	298 (52.5)	630 (48.9)	
Mean Age, years (SD)	9.59 (2.2)	10.35 (2.4)	<0.001
Ethnicity			
Caucasian	507 (91)	1083 (85.6)	0.001
Non-Caucasian	50 (9)	182 (14.4)	
Maternal Education			
High school or less	176 (87.1)	405 (86)	0.693
Any post-secondary Education	26 (12.9)	66 (14)	
Paternal Education			
High school or less	198 (70)	511 (76.7)	0.028
Any post-secondary education	85 (30)	155 (23.3)	
Hx of Early childhood illness			
Yes	147 (25.9)	347 (26.9)	0.634
No	421 (74.1)	941 (73.1)	
Asthma Status			
Ever Asthma	87 (15.5)	184 (14.4)	0.553
No Asthma	474 (84.5)	1090 (85.6)	
Maternal history of Asthma			
Yes	47 (8.6)	112 (9.2)	0.674
No	502 (91.4)	1108 (90.8)	
Paternal history of Asthma			
Yes	54 (10.4)	87 (7.6)	0.051
No	464 (89.6)	1065 (92.4)	
Maternal History of allergic diseases			
Yes	167 (30.4)	316 (25.9)	0.051
No	383 (69.6)	904 (74.1)	

Paternal History of allergic diseases Yes No	 124 (23.9) 394 (76.1)	 276 (24) 876 (76)	 0.993
Mother Currently Smoking Yes No	 113 (20) 451 (80)	 264 (20.7) 1010 (79.3)	 0.737
Father Currently Smoking Yes No	 157 (27.9) 406 (72.1)	 319 (25.1) 951 (74.9)	 0.212
Daycare Attendance Yes No	 325 (57.8) 237 (42.2)	 672 (52.7) 603 (47.3)	 0.042
Cat in the home Yes No	 52 (9.8) 477 (90.2)	 131 (11) 1065 (89)	 0.485
Presence of musty smell of mold/ mildew in the home Yes No	 127 (23) 424 (77)	 217 (17.5) 1026 (82.5)	 0.006
Presence of mold/mildew in the home Yes No	 113 (19) 450 (79.9)	 238 (18.6) 1042 (81.4)	 0.457
House heating type Natural gas Other	 422 (74.6) 144 (25.4)	 921 (72.3) 353 (27.7)	 0.312
Air filter in the home Yes No	 217 (41.7) 303 (58.3)	 537 (46.7) 614 (67)	 0.061
Humidifier in the home Yes No	 138 (26.6) 381 (73.4)	 296 (26) 843 (74)	 0.796
Presence of wood fireplace in the home Yes No	 83 (16.1) 434 (83.9)	 224 (19.5) 923 (80.5)	 0.091

Table 2: Descriptive Statistics of the study population and farming exposures comparing those who were included in lung function testing to those who were excluded

Variables	Included in Analysis (N = 568) n (%)	Excluded from the Analysis (N = 1288) n (%)	P value
Home location			
Farm	308 (54.5)	726 (57.1)	0.299
Non-farm	257 (45.5)	545 (42.9)	
Farm type			
Livestock farm	124 (77.5)	91 (24.9)	0.549
Non livestock farm	36 (22.5)	274 (75.1)	
Mother lived on farm while pregnant			
Yes	179 (31.9)	403 (31.6)	0.901
No	383 (68.1)	874 (68.4)	
Visited a farm			
Regularly	333 (66.2)	436 (39.5)	0.030
Never/Not regularly	170 (33.8)	669 (60.5)	
Consumption of unpasteurized milk in first year of life	15 (2.7)	39 (3.1)	0.631
Yes	544 (97.3)	1220 (96.9)	
No			
Lived on farm in first year of life			
Yes	173 (30.6)	397 (30.9)	0.890
No	392 (69.4)	886 (69.1)	
Haying or moving or playing with hay bales	132 (23.7)	249 (19.7)	0.055
Regularly	426 (76.3)	1016 (80.3)	
Not Regularly			
Feeding livestock			
Regularly	148 (26.6)	274 (21.7)	0.024
Not Regularly	409 (73.4)	987 (78.3)	
Cleaning or playing in barns			
Regularly	128 (22.9)	210 (16.6)	0.001
Not Regularly	430 (77.1)	1054 (83.4)	

Emptying or filling grain bins Regularly Not Regularly	46 (8.2) 512 (91.8)	82 (6.5) 1178 (93.5)	0.182
Cleaning or playing in pens and corrals Regularly Not Regularly	120 (21.5) 437 (78.5)	195 (15.5) 1066 (84.5)	0.002
Riding horses Regularly Not Regularly	48 (8.6) 510 (91.4)	149 (11.8) 1113 (88.2)	0.042

Table 3: Mean* Pulmonary Function Results by Asthma Status and Farming activities and home location Variables

Variables	FEV_1 (Litres)	FVC (Litres)	FEV_1/FVC (%)	FEF (25 – 75%) (Litres/Second)
Asthma status				
Absent	2.21(2.19-2.41)	2.52(2.49-2.55)	0.88(0.87-0.88)	2.62(2.56-2.68)
Present	2.17(2.11-2.23)	2.53(2.46-2.60)	0.85(0.84-0.87)	2.41(2.27-2.54)
p-value	(p=0.177)	(p=0.825)	(p=0.005)	(p=0.005)
Home location				
Farm	2.22 (2.19-2.26)	2.56(2.45-2.52)	0.86(0.85 –0.87)	2.56 (2.48 -2.64)
Non-Farm	2.19 (2.16-2.22)	2.48(2.45- 2.52)	0.88(0.85– 0.89)	2.60(2.53– 2.67)
p-value	(p =0.155)	(p=0.009)	(p=0.006)	(p = 0.491)
Haying				
Regularly	2.21 (2.16–2.26)	2.53(2.47–2.59)	0.87(0.86-0.88)	2.59 (2.48–2.70)
Not Regularly	2.20(2.17– 2.23)	2.52(2.48– 2.55)	0.87(0.87– 0.88)	2.57(2.51– 2.63)
p-value	(p=0.865)	(p=0.667)	(p=0.809)	(p=0.713)
Feeding livestock				
Regularly	2.22(2.17–2.27)	2.55(2.49– 2.60)	0.86(0.85– 0.87)	2.60(2.49– 2.70)
Not Regularly	2.20 (2.17–2.23)	2.51 (2.48– 2.54)	0.87(0.87– 0.88)	2.57(2.51– 2.63)
p-value	(p= 0.473)	(p =0.247)	(p =0.090)	(p =0.680)
Cleaning/playing in barns				
Regularly	2.21(2.16-2.26)	2.56(2.50–2.62)	0.87(0.85–0.88)	2.56(2.45-2.68)
Not Regularly	2.20(2.17–2.23)	2.51(2.48– 2.54)	0.87(0.87–0.88)	2.58(2.52– 2.64)
p-value	(p =0.675)	(p=0.131)	(p=0.454)	(p=0.819)
Emptying/Filling grain bin				
Regularly	2.26(2.18– 2.35)	2.67(2.58–2.78)	0.85(0.83–0.87)	2.58(2.36–2.80)
Not Regularly	2.20 (2.17–2.22)	2.51(2.48–2.53)	0.87(0.87 –0.88)	2.60(2.53–2.66)

p-value	(p =0.156)	(p=0.001)	(p=0.035)	(p=0.876)
Cleaning/playing in pens or corrals				
Regularly	2.23(2.18–2.28)	2.56(2.50–2.62)	0.87(0.86-0.88)	2.70(2.56-2.83)
Not Regularly	2.19(2.17–2.22)	2.51(2.48–2.54)	0.87(0.86–0.88)	2.56(2.49–2.63)
p-value	(p =0.249)	(p=0.176)	(p=0.945)	(p=0.086)
Riding horses				
Regularly	2.20(2.11–2.29)	2.56(2.49 –2.55)	0.86(0.84–0.88)	2.52(2.30–2.73)
Not regularly	2.20(2.18–2.23)	2.56(2.46–2.65)	0.87(0.87–0.88)	2.60(2.54–2.67)
p-value	(p=0.921)	(p=0.456)	(p=0.297)	(p=0.449)

* These are adjusted means using ANCOVA after adjustment for age, sex, and height

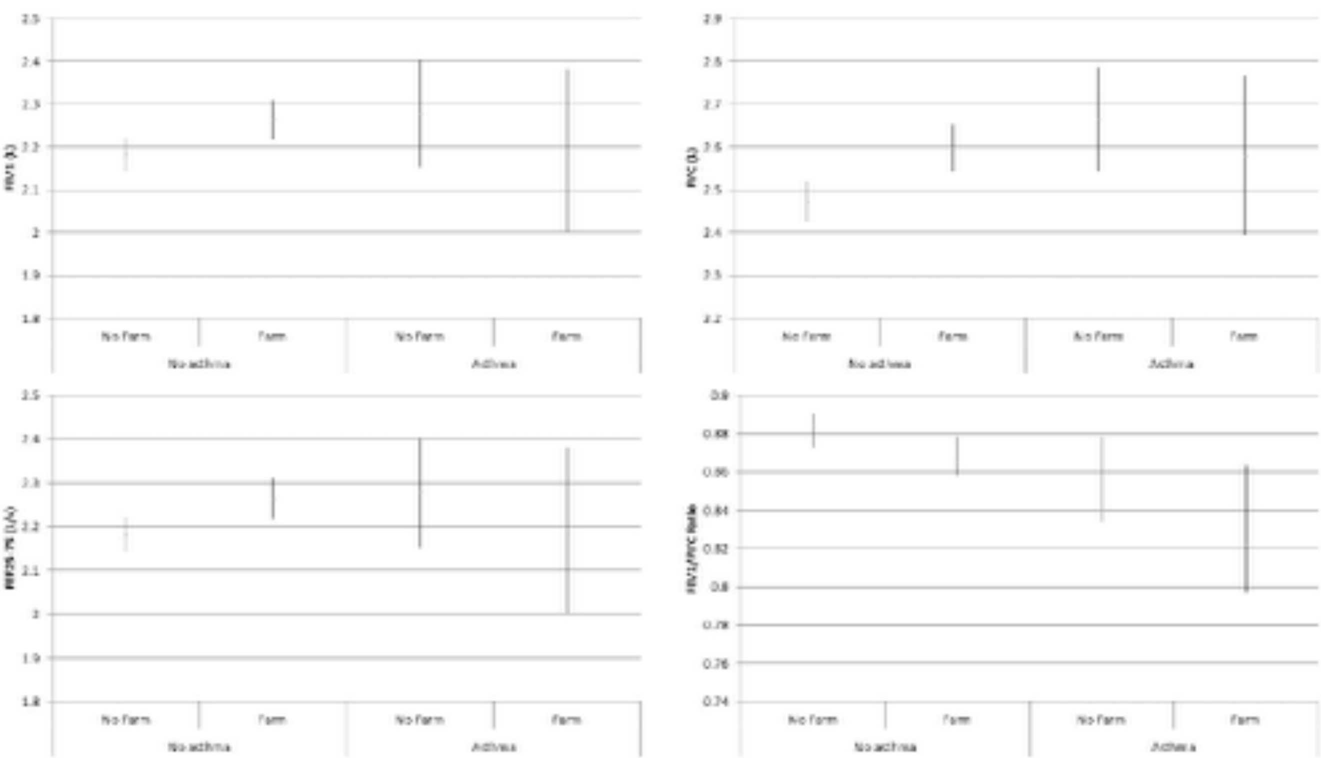
Table 4: Adjusted Association between Home Location, Farming Activities and Early Life Farming Exposure Variables with Lung Function Outcomes*

Primary Variable	FEV_1		FVC		FEV_1/FVC		FEF	
		p-value		p-value		p-value		p-value
Live on Farm	0.079 (0.033)	0.017	0.110 (0.039)	0.005	-0.013 (0.008)	0.102	0.031 (0.070)	0.660
Haying, moving, or playing w/ hay bales regularly	-0.004 (0.034)	0.898	0.006 (0.040)	0.880	0.000 (0.008)	0.974	-0.014 (0.071)	0.844
Feeding livestock regularly	0.014 (0.032)	0.650	0.032 (0.037)	0.398	-0.014 (0.008)	0.068	-0.009 (0.067)	0.890
Cleaning or playing in bins regularly	0.021 (0.033)	0.527	0.060 (0.039)	0.120	-0.004 (0.008)	0.604	-0.027 (0.070)	0.695
Emptying or filling grain bins regularly	0.044 (0.050)	0.381	0.163 (0.058)	0.005	-0.031 (0.012)	0.008	-0.109 (0.105)	0.299
Cleaning or playing in pens and corrals regularly	0.037 (0.034)	0.282	0.041 (0.041)	0.317	-0.004 (0.008)	0.646	0.055 (0.073)	0.452
Riding horses regularly	-0.004 (0.048)	0.933	0.035 (0.057)	0.539	-0.011 (0.012)	0.357	-0.040 (0.103)	0.698
Farm type (Non Livestock vs/livestock)	0.051 (0.071)	0.475	0.054 (0.080)	0.500	0.033 (0.018)	0.070	0.091 (0.140)	0.519

Mother lived on farm while pregnant	0.030 (0.031)	0.0332	0.029 (0.037)	0.433	-0.002 (0.007)	0.837	0.097 (0.065)	0.139
Visited farm regularly	-0.041 (0.031)	0.187	0.006 (0.037)	0.868	-0.011 (0.006)	0.089	-0.106 (0.066)	0.111
Consumption of unpasteurized milk in first year of life	0.122 (0.092)	0.188	0.109 (0.109)	0.319	0.006 (0.022)	0.798	0.340 (0.193)	0.079
Lived on farm in first year of life	0.049 (0.031)	0.114	0.051 (0.037)	0.167	-0.003 (0.008)	0.707	0.110 (0.066)	0.098

*Adjusted for the following: Age, Sex, Height, Childhood Illness, Paternal Hx of Asthma, Maternal Hx of Asthma, Maternal Hx of Allergy, Mother Ex Smoker,, Mother Current Smoker, Daycare Attendance, Presence of Cat in the home, Signs of Mold in the home, Mold/Mildew present in the home, Wood Fireplace in the home, Air Filter in the home, Humidifier in the home

Figure 4: Adjusted mean lung function (SE) by asthma status and farm location



CHAPTER 5:

SUMMARY OF RESULTS AND DISCUSSION

5.1 Summary of Results

The primary aim of this thesis was to evaluate rural exposures and pulmonary function in a rural pediatric population and examine the relationship between them. We considered the following research questions: (1) What are levels of pulmonary function in a rural population of children?; (2) Are there differences in pulmonary function between farm and non-farm dwelling children? and; (3) Are certain types of farming activities associated with pulmonary function after adjusting for potential confounders and is there interaction between these activities and sex or asthma status?

The primary findings of this thesis were:

-Overall, the population under study had good pulmonary function.

-There were differences in pulmonary function between farm and non-farm dwelling children where farm children had better lung function based on FVC and FEV_1.

-Despite higher FEV_1 and FVC among farm dwelling children, FEV_1/FVC ratio was lower compared to non-farm dwelling children.

-Certain types of farming activities were associated with differences in pulmonary function.

-Higher FVC was seen with emptying and filling grain bins regularly.

-Increased FEV_1/FVC was seen with feeding livestock regularly.

-Lower FEV_1/FVC was seen with regularly emptying and filling grain bins.

-Pulmonary function levels were also different between early life farming exposures including higher FEV_1 seen with mother living on farm while pregnant.

-There was effect modification of some of these associations by asthma status.

- Higher FVC was seen with living on a farm among those without asthma.

-Higher FEV_1/FVC was seen with feeding livestock regularly among those without asthma.

- Lower FVC was seen with farm type (livestock or non-livestock) among those without asthma.

-Lower FEV_1/FVC was seen with emptying and filling grain bins regularly among those without asthma.

-Lower FEF_{25-75} was seen with living on a farm in the first year of life among those with asthma.

-No effect modification of these associations by sex was seen.

Secondary findings from this thesis included:

-Certain environmental and behavioural factors were associated with differences in levels in pulmonary function.

These included:

- Higher FVC was seen with negative maternal allergy history and absence of cat in home;
- Lower FEV_1/FVC was associated with early childhood illness and with signs of mold smell;
- Higher FEV_1/FVC was also seen with no previous asthma diagnosis, previous childhood illness history, no previous bronchitis history, no previous pneumonia history, positive maternal allergy history, mother never smoking, mother not currently smoking, absence of mold/mildew in home, house heating type other than natural gas, and absence of wood fireplace in home.

5.2 Discussion

Certain types of farming and farming activities have been shown to be protective against asthma including livestock farming and activities including livestock, riding horses, and cleaning or playing in pens/corrals (28-33) Grain-farming activities were associated with higher rates of asthma. (28-33) Findings from this thesis complement previous findings and are in keeping with the major findings in the current literature.

Early life farming exposures including mother living on farm while pregnant was associated with pulmonary function measures in our study. Some of these early life exposures were close to statistically significant associations with pulmonary function. This included consumption of unpasteurized milk in the first year of life. While these have been predictors of the presence of asthma, they may not predict pulmonary function.(11, 33-41) This may be because of differential reaction to exposures and timing of exposure compared to timing of pulmonary function development and testing.

We could not assess for true dose-response in our study. This may be a potential direction for future studies, to determine the dose-response relationship between farming exposures and pulmonary function.

Children with asthma may also experience differential reaction to certain exposures. (26-28, 32-41) They may be more sensitive to pro-inflammatory effects due to hyper-responsive airways and inflammatory airway changes secondary to their asthma. (26-28, 32-41) Interaction between various farming exposures and asthma status was observed. One may also expect the presence or absence of asthma diagnosis to influence types of activities in which children may be allowed to participate. Parents may elect to have their children with asthma avoid asthma triggers or strenuous activities. Those with a positive asthma diagnosis may not participate in or with similar frequency as children without asthma. Despite these facts, trends towards higher FEV_1 and FVC were seen with living on a farm in the first year of life suggesting that the differences in pulmonary function seen with farm dwelling may not be purely due to reverse causality.

Pulmonary function differed between farm and non-farm dwelling children where higher pulmonary function was seen with farm dwelling. The exposures from a farm dwelling home location may explain the differences in pulmonary function seen in our study. Early life farming exposures may allow for sensitization and immunologic response with a protective benefit or increased tolerance to environmental triggers or exacerbating factors for asthma. As a result, pulmonary function is not impacted by future or further exposure. Whereas, the non-farm dwelling children may not have the initial exposure to these triggers and mount as strong a response in their respiratory health development. This, in turn, would result in adverse response to the environmental triggers and a reduction in respiratory health as a result. This may also explain why emptying grain bins was associated with higher FEV_1 and FVC compared to not regularly participating. This contrasts with the current literature where grain-farming activities are found to be associated with asthma or worse respiratory health.

5.3 Assessment of selection bias

With regards to potential limitations of the study, there may be selection bias. There were more children with parents with higher education or who had a history of asthma or allergic disease among those included compared to those excluded from the study based on the full cross-sectional survey phase of the SRHS. Thus, children in healthier environments or influenced by healthier behaviours as modeled by parents may have been more inclined to participate. Despite this, the overall population of children was healthy, based on average lung function values. To assess for presence of this bias, we ran a descriptive analysis of the children who participated in the clinical study and those that did not. There was no statistically significant difference between them with regard to respiratory outcomes. Therefore, any selection bias effect should be negligible. Also, the purpose of the study was to investigate associations between farming exposures and the outcomes of lung function. Since the purpose was more etiologic in nature, the associations we observed were likely to be valid, at least internally.

5.4 Assessment of information bias

Invalid or imprecise study measures may lend to the collection of erroneous data resulting in misclassification. To limit this form of bias, the use of a validated collection tool, like a survey or questionnaire, and an objective measure like pulmonary function, is important. Use of a validated and well-structured questionnaire allows for collection of significant and pertinent data in a less biased manner. Using objective, clinical measures including pulmonary function testing also adds validity and strength to our research findings. It is a reliable measure where results can be replicated with repeat testing and does not depend on subjective assessment or reporting.

Potential bias can arise from the process of data collection. The data was collected from a questionnaire survey that was answered by the children's parents. As a result, it is possible for error in information recall. However, the questionnaire that was utilized was validated and used in other studies.

5.5 Assessment of confounding

Lung function is a complex phenomenon. There are potential confounders that may not be known or easily accounted for as a result. To reduce the potential for confounding, known important potential confounders were taken into account during the model building process by using multivariable analysis. These variables are based on known factors from the literature. Planning for and measuring these variables can account for and limit confounding. We also fitted the model based on confounding in the data, which was done by including variables in the model building that were statistically significant or affected the results of other variables included in the model. Each variable was added individually to the model to assess its influence on the other variables in the model. This was done with multiple regression models that were fitted using linear regression for continuous outcomes (e.g. lung function measures).

5.6 Interaction

There was statistical interaction found between asthma status and certain farming activities and with living on a farm. Higher FEV_1 and FVC were seen with living on a farm among those without asthma. Lower FEV_1/FVC was seen with feeding livestock regularly among those without asthma. Higher FVC and lower FEV_1/FVC ratio were also seen with emptying grain bins regularly among those without asthma.

When considering interaction between sex and farming exposures, no statistically significant interaction was found.

5.7 External Validity

Our study and its findings may have select or limited applications outside our clinical population. However, the results of our study could be applied to other similar populations in rural areas of Canada or with similar farming practices and exposures.

The population was sampled from different rural quadrants of Saskatchewan, which allows for geographical variance and better representation of the Saskatchewan rural population.

The majority of children who participated in the study were Caucasian. The results of the study may have limited translation or applicability for populations with different demographics, such as non-Caucasian children. Further study with a more varied population may provide more information on potential applicability. Farming practices may also vary based on geographic and climate from region to region within a country or internationally.

5.8 Additional Potential Limitations

We used a fixed population from the Saskatchewan Rural Health Cohort Study, which could present problems with statistical power. A power calculation was performed and confirmed the study population was adequate to see a moderate effect for our associations of interest. Also, we found statistically significant associations with strengths of associations that we expected suggesting that statistical power issues were minimal to negligible.

We could not draw causal associations between exposures and outcomes. Temporality could not be assessed as this was an observational study with a cross-sectional design preventing us from determining the timing of exposure and the effect on pulmonary function. Future studies, including those with data from the SRHS over time, may allow for an assessment of temporality.

5.9 Strengths of the Study

The study also has many strengths. The population was from the SRHS which sampled different rural quadrants of Saskatchewan. This allows for geographical variance within the study population and better representation of the rural population in Saskatchewan. Use of a validated and well-structured questionnaire allows for collection of significant and pertinent data in a less biased fashion. Using objective, clinical measures including pulmonary function testing also adds validity and strength to our research findings.

To improve safety, acceptability, and validity of the pulmonary function testing, children were excluded if they had recent a cough or cold, use of short-acting asthma inhaler within the last two hours, recent use of an allergy pill or cough syrup or headache on the day of testing. Children were rescheduled where appropriate. To limit reporting bias regarding a patient's asthma status, the questionnaire was completed prior to the pulmonary function testing.

5.10 Recommendations, applications, and future research directions

Given the discrepancies in the literature on rural asthma, our study helps in filling some of the gaps in the current knowledge. We have provided information and further understanding into asthma severity as it applies to the pediatric population in rural and farming areas. Our study used pulmonary function testing as an objective measure of respiratory health. In the long term, future research, building on this work could have applications that have a significant impact at the provincial, national and international level regarding current asthma prevention, diagnosis, and treatment. Pulmonary function testing can be utilized to assess or to predict respiratory health. Changes in pulmonary function can be seen with asthma. Pulmonary function testing can allow for a better estimation of asthma severity. This can impact diagnosis and in turn treatment or management of asthma. Asthma severity may be better reflected by changes in pulmonary function compared to symptoms as reported by patients. Further research using objective measures like pulmonary function may help identify the true severity of asthma. This would allow for better therapy and earlier intervention for medical therapy, which in turn, could help guide practice guidelines and potential studies for intervention and prevention.

Regarding future directions for research on pulmonary function and asthma epidemiology, there are several potential lines of research. To better delineate the relationship or direction of exposures leading to disease, further research looking at timing of exposures in relation to the development of lung function. Longitudinal studies may be a more effective study design to assess this issue.

Many studies have been conducted with different populations regarding farming exposures and respiratory health. These studies are limited by their total number of participants. This limits the power of the conclusions on causality that can be drawn from such studies. By pooling these studies through meta-analysis, the power may be improved and a better understanding of causal relationships between exposures and respiratory health can be drawn. The majority of previous studies are questionnaire based only. Our study adds unique data to the current literature by utilizing the clinical measure of pulmonary function.

Our study population was predominantly Caucasian due to the demographic makeup of the area and population under study. To determine whether the results of our study could be extrapolated or generalized to be applied to other populations, further studies involving rural and farming populations with more diverse ethnic or demographic makeup would be an important direction for further research.

5.11 Conclusion

In conclusion, findings from this study suggest that there is a difference in pulmonary function between farm and non-farm dwelling children in our Saskatchewan population. We provided new evidence regarding pediatric pulmonary function through comparison of the study population by demographic, home dwelling and farming behavior and exposures. This is novel information that can complement the current and ongoing research into pediatric pulmonary health and pediatric asthma. Future studies may focus on pulmonary function and asthma severity in the pediatric population and if differences may exist when the populations are compared by similar factors including sex, home dwelling, and farming exposures.

REFERENCES

1. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach, update 2010.

2. Canadian Institute for Health Information. Respiratory Disease in Canada. Statistics Canada;2001.

3. Ismaila A, et al. Clinical, economic, and humanistic burden of asthma in Canada: a systemic review *BMC Pulmonary Medicine* 2013, 13:70 10.1186/1471-2466-13-70

4. Rabe et al. Worldwide severity and control of asthma in children and adults: The global Asthma Insights and Reality Surveys. Journal of Allergy and Clinical Immunology. 2004

5. Lung disease imposes major costs on Canada's Economy. The Conference Board of Canada, New Release. March 2012

6. J. Lawson et al. Urban-rural differences in asthma prevalence among young people in Canada: the roles of health behaviours and obesity. Annals of Allergy, Asthma, and Immunology. 2011

7. Valet et al. High Asthma Prevalence and increased morbidity among rural children in Medicaid cohort. Annals of Allergy, Asthma, and Immunology. 2011

8. R. Garner and D. Kohen. Changes in the prevalence of asthma in Canadian children. Statistics Canada Catalogue no. 82 – 003 – X Health Reports. June 2008 (Vol. 19 No. 2)

9. Priftis, K. et al. Different effects of urban and rural environments in the respiratory status of Greek schoolchildren. Respiratory Medicine 2007. 101; 98-10

10. Chrischilles E, et al. Asthma prevalence and morbidity among rural Iowa school children. Journal of Allergy and Clinical Immunology 2004; 113:66–71.

11. Barry RJ, et al. Factors contributing to risks for pediatric asthma in rural Saskatchewan. Annals of Allergy, Asthma and Immunology 2012

12. MacNeill SJ, et al. Asthma and allergies: is the farming environment (still) protective in Poland? The GABRIEL Advanced Studies. Allergy 2013; 68: 771–779

13. Midodzi WK, Rowe BH, Majaesic CM, Senthilselvan A. Reduced risk of physician-diagnosed asthma among children dwelling in a farming environment. *Respirology* 2007; 12(5):692-9.

14. Reidler et al. Allergic diseases and atopic sensitization in children related to farming and anthroposophic lifestyle – the PARSIFAL study. Allergy 2006; 61:414–421.

15. Farthing , et al. Farming Activities and Respiratory Health in School Age Children. 2007

16. Stout J, et al. Classification of Asthma Severity in Children: The Contribution of Pulmonary Function Testing. Arch Pediatrics. 2006

17. Kemp T, Pearce N, Crane J, Beasley R. Problems of measuring asthma prevalence. *Respirology* 1996;1(3):183-8.

18. Canadian Thoracic Society. Canadian Asthma Consensus Guidelines. 2010

19. Voter et al. Pulmonary Function Testing in Childhood Asthma. Immunology and Allergy Clinics of North America.

20.Canadian Thoracic Society 2012 guideline update: Diagnosis and management of asthma in preschoolers, children and adults.

21. Ali et al. Single-breath counting: a pilot study of a novel technique for measuring pulmonary function. Am J Emerg Med. 2011. Jan;29(1): 33-36.

22. Bahadori K,et al. Economic Burden of Asthma: Systematic Review. BMC Pulmonary Medicine 2009.

23. Sadatsafavi M, et al. Direct health care costs associated with asthma in British Columbia. Canadian Respiratory Journal. 2010 Mar-Apr; 17(2); 74-80.

24. Asher, et al. International Study of Asthma and Allergies in Children (ISAAC): Rationale and Methods. Journal of European Respirology 1995. 8; 483 – 491

25. Weiland, et al. Phase II of the International Study of Asthma and Allergies in Children (ISAAC II): Rationale and Methods. Journal of European Respirology 2004. 24; 406-412

26. Lawson, J., et al. Regional variations in risk factors for asthma in school children. *Can Respir J* 2005; 12(6):321-6.

27. Rennie, D., et al. Differences in respiratory symptoms and pulmonary function in children in 2 Saskatchewan communities. *Annals of Allergy and Asthma Immunology* 2004; 92(1):52-9.

28. Lawson, J., et al. Occurrence of newonset wheeze in a 3-year follow-up study of schoolchildren. *Ann Allergy Asthma Immunol* 2007;99(6):502-8.

29. Asher et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in children. ISAAC Phases I and III repeat multi-country cross-sectional surveys. Lancet 2006. 368; 733-743

30. Asher M, et al. The International Study of Asthma and Allergies in Childhood (ISAAC).ISAAC Steering Committee. *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology* 1998;28:52

31. Von Mutius, et al. Exposure to endotoxin or other bacterial components might protect against the development of atopy. Clinical Exp Allergy: 2000; 30: 1230-4..

32. Lawson, J., et al. Relationship between indoor environment and asthma and wheeze severity among rural children and adolescents. *Journal of Agromedicine* 2009;14(2):277-85.

33. Douwes J, et al. Farm exposure in utero may protect against asthma,hay fever and eczema. Journal of European Respirology 2008; 32:603–611.

34. Ege MJ, et al. Not all farming environments protect against the development of asthma and wheeze in children. Journal of Allergy and Clinical Immunology 2007;119: 1140–1147.

35. Wickens K, et al. Farm residence and exposures and the risk of allergic diseases in New Zealand children. Allergy 2002;57:1171–1179.

36. Radon K, et al. Farming exposure in childhood, exposure to markers of infections and the development of atopy in rural subjects. Clin Exp Allergy 2004; 34:1178–1183.

37. Remes ST, et al. Which factors explain the lower prevalence of atopy amongst farmers' children? Clin Exp Allergy 2003; 33:427–434.

38. Viinanen A, et al. The protective effect of rural living against atopy in Mongolia. Allergy 2007; 62:272–280.

39. Remes ST, et al. Does heredity modify the association between farming and allergy in children? Acta Paediatr 2002; 91:1163–1169.

40. Downs SH, et al. Having lived on a farm and protection against allergic diseases in Australia. Clin Exp Allergy 2001; 31:570–575.

41. Dimich-Ward H, Chow Y, Chung J, Trask C. Contact with livestock--a protective effectagainst allergies and asthma? *Clin Exp Allergy* 2006; 36(9):1122-9.

42. Bröms et al. Effect of degree of urbanisation on age and sex-specific asthma prevalence in Swedish preschool children. BMC Health. 2009

43. Glover et al. Preventable Asthma Episodes Among Urban/Rural Children and Adolescents: A Comparitive Study. Journal of Health Disparities Research and Practice. 2010

44. Standardization of Spirometry – 1987 Update. Statement of the American Thoracic Society. American Review of Respiratory Disease. 1987

45. Ferris et al. ATS Epidemiology development. Thorax. 1978

46. Ostrowski, W. Factors influencing lung function: Are the predicted values for spirometry reliable enough? Journal of Physiology and Pharmacology 2006. 57, Supp 4, 263-271

47. Pahwa P, et al. Saskatchewan Rural Health Study. BMC Research Notes 2012.

48. Pellegrino et al. Interpretive strategies for lung function tests. European Respirology Journal. 2005. 26: 948-968

49. Olawale et al. Relationships between Plasma Micronutrients, Serum IgE, and Skin Test Reactivity and Asthma among School Children in Rural Southwest Nigeria J Biomark. 2014; 2014: 106150

50. Hosmer D, and Lemenshow S. A Review of Goodness of Fit Statistics for Use in the Development of Logistic Regression Models. American Journal of Epidemiology 1982. 115(1): 92 – 106.

51. Coates A. et al. Spirometry in Primary Care. Canadian Respiratory Journal 2013. 20(1): 13-22.

Appendix A: Additional Tables

Interaction Table 1: Sex Interaction with Main Effects

Interaction Term		FEV		FVC		FEV/FVC		FEF	
		Stratified	p-value	Stratified	p-value	Stratified	p-value	Stratified	p-value
Child Age * Sex	(M)	0.005	0.004 **	0.023	<0.005 **	-0.008	0.015 **	-0.011	0.032 **
	(F)	0.013		0.014		0.001		0.025	
Child Height * Sex	(M)	0.039	0.003 **	0.047	<0.005 **	0.000	0.024 **	0.037	0.058 **
	(F)	0.016		0.021		-0.001		0.017	
Asthma Dx * Sex	(M)	-0.068	0.678	-0.016	0.286	-0.026	0.431	-0.221	0.359
	(F)	0.020		0.042		-0.003		-0.003	
Childhood Illness * Sex	(M)	0.023	0.032 **	0.020	0.016 **	0.000	0.344	0.014	0.780
	(F)	-0.033		-0.001		-0.018		-0.111	
Mat Hx of Asthma * Sex	(M)	-0.029	0.138 **	-0.184	0.160 **	0.043	0.790	0.321	0.147 **
	(F)	-0.059		-0.050		-0.004		-0.156	
Mat Hx of Allergy * Sex	(M)	0.019	0.198 **	0.154	<0.005 **	-0.031	0.003 **	-0.209	0.006 **
	(F)	0.007		-0.013		0.002		0.043	
Par Hx of Asthma * Sex	(M)	-0.002	0.123 **	0.050	0.029 **	-0.019	0.305	-0.224	0.588
	(F)	-0.032		-0.036		0.002		-0.056	
Mat ExSmoker * Sex	(M)	0.085	0.043 **	0.045	0.010 **	-0.027	0.759	0.127	0.880
	(F)	-0.016		0.000		-0.013		-0.076	
Mat CurrentSmoker * Sex	(M)	-0.117	0.043 **	-0.091	0.010 **	0.032	0.759	-0.160	0.880
	(F)	-0.016		0.009		-0.013		-0.076	
Daycare * Sex	(M)	0.006	0.172 **	0.038	<0.005 **	-0.010	0.023 **	-0.033	0.031 **
	(F)	0.040		0.021		0.005		0.052	
Cat in home * Sex	(M)	-0.021	0.011 **	-0.014	0.001 **	-0.004	0.879	-0.019	0.765
	(F)	-0.048		-0.044		-0.009		-0.101	
Signs of Mold * Sex	(M)	-0.029	0.262	0.034	0.016 **	-0.019	0.106 **	-0.142	0.257
	(F)	-0.037		-0.019		-0.005		-0.100	
Mold/Mildew * Sex	(M)	-0.100	0.832	-0.094	0.242 **	-0.006	0.130 **	-0.182	0.099 **
	(F)	0.002		0.021		0.001		-0.001	
Interaction Term		FEV		FVC		FEV/FVC		FEF	
		Stratified	p-value	Stratified	p-value	Stratified	p-value	Stratified	p-value
Wood Fireplace * Sex	(M)	0.027	0.296	-0.017	0.422	0.006	0.370	0.175	0.239 **
	(F)	0.024		0.055		-0.017		-0.077	
Air Filter * Sex	(M)	-0.033	0.263	-0.009	0.005 **	-0.001	0.383	-0.096	0.113 **
	(F)	0.020		0.025		-0.005		0.005	
Househeating Type * Sex	(M)	-0.077	0.918	-0.063	0.099 **	-0.007	0.254	-0.107	0.046 **
	(F)	0.014		0.011		-0.004		0.031	
Humidifier * Sex	(M)	-0.068	0.678	-0.016	0.286	-0.026	0.431	-0.221	0.359
	(F)	0.020		0.042		-0.003		-0.003	

Appendix B: Ethics Approval

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
James A. Dosman	Canadian Centre for Health and Safety in Agriculture	10-177

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
University of Saskatchewan
Saskatoon SK

SUB-INVESTIGATOR(S)
Donna Rennie, John R. Gordon, Josh Lawson, Shelley Kirychuk, Niels Koehncke, Bonnie Janzen, Roland F. Dyck, Ambikaipakan Senthilselvan, Yue Chen, William Pickett, Roger Pitblado, Punam Pahwa

SPONSORING AGENCIES
CANADIAN INSTITUTES OF HEALTH RESEARCH (CIHR)

TITLE
Saskatchewan Rural Health Study – Stage 5 Children's Cohort

ORIGINAL REVIEW DATE	APPROVED ON	APPROVAL OF	EXPIRY DATE
18-Oct-2010	12-Nov-2010	Researcher's Summary (10-Nov-2010) Attachment #1: Revised Invitation to participate and information letter (parent) Attachment #3: Revised Reminder Letter Attachment #4: Revised Parental Information and Consent Form Attachment #5: Revised Participant Information & Assent Form	12-Nov-2011

Full Board Meeting ☒ Date of Full Board Meeting: 18-Oct-2010

CERTIFICATION
The study is acceptable on scientific and ethical grounds. The Bio-REB considered the requirements of section 29 under the Health Information Protection Act (HIPA) and is satisfied that this study meets the privacy considerations outlined therein. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face) meeting. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://www.usask.ca/research/ethics_review/.

REB ATTESTATION
In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board has been approved by the Minister of Health, Province of Saskatchewan, to serve as a Research Ethics Board (REB) for research projects involving human subjects under section 29 of The Health Information Protection Act (HIPA).

Michel Desautels, Ph.D., Chair
University of Saskatchewan
Biomedical Research Ethics Board

Please send all correspondence to:

Research Ethics Office
University of Saskatchewan
Box 5000 RPO University
1607 – 110 Gymnasium Place
Saskatoon, SK Canada S7N 4J8